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10/08/2021 11:10:23
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The journal has been partly supported by the Korean Federation of Science and Technology Societies. KJA is indexed/tracked/covered by SCIE (Science Citation Index Expanded), KCI (indexed by the National Research Foundation of Korea), PubMed, PubMed Central, EBSCOhost Databases, KoreaMed, KoMCI Web, KoreaMed Synapse, Science Central, SCOPUS, Embase, CAS (Chemical Abstracts Service), WPRIM (Western Pacific Regional Index Medicus), DOI, DOAJ (Directory of Open Access Journal) and Google Scholar. It has been indexed in MEDLINE by U.S. National Library of Medicine.

Korean Journal of Anesthesiology Volume 75, Number 1, 3 February 2022

The circulation number per issue is 400.

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Printed by M2PI
8th Fl, DreamTower, 66 Seongsui-ro, Seongdong-gu, Seoul 04784, Korea
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Myocardial injury in noncardiac surgery

Jungchan Park, Jong-Hwan Lee

Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

심근 손상은 허혈성 증상의 유무와 관계없이 심근 트로포닌(cardiac troponin, cTn) 수치의 상승으로 정의된다. 관련 연구에서 비심장 수술에서 수술 후 심근 손상이 사망률을 증가시킨다는 확실한 증거와 함께 비심장 수술 후 심근 손상(myocardial injury after noncardiac surgery, MINS)의 진단 기준으로 비허혈성 병인의 증거 없이 수술 후 30일 이내의 cTn 수치의 상승이 제시되었다. 대부분의 MINS는 허혈성 증상을 보이지 않으며, 주술기 기간 동안의 산소의 수요와 공급의 불일치로 인해 발생한다. 이러한 발생 기전을 고려하여 MINS의 예측에 일반적인 심장 위험도 계층화의 모델이 도입되었고, 알려진 위험요인 중 병행 질환, 변형, 혈당 수치 및 수술 중 저혈압 등이 실제로 MINS와의 연관성을 보였다. 이 요인들을 조절하여 MINS 예방이 도출될 수 있다는 연구 결과 또한 있으나, 이에 대해서는 추가적인 연구가 필요한 실정이다. 최근 지침에서는 대부분의 MINS 환자가 증상을 보이지 않기 때문에 고위험 환자에서는 MINS의 발생 가능성이 가장 높은 수술 후 첫 48시간 동안 cTn 수치를 정기적으로 모니터링할 것을 권장한다. 아스피린, 항고혈압제, 스타틴과 같은 심혈관약물 또한 MINS 환자들에게서 효과를 보였다. 무작위 대조 시험에서는 직접경구항응고제(direct oral anticoagulant)가 MINS와 연관된 사망률의 감소를 보여주었다. 비심장 수술에서 수술 전부터 발견된 심근 손상 또한 수술 후 사망률과 관련이 있는 것으로 밝혀졌으며, 이에 대한 후속 연구 또한 필요하다.

Keywords: Mortality; Patient outcome assessment; Postoperative complications; Postoperative period; Troponin I; Troponin T.

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Efficacy of interventional treatment strategies for managing patients with cervicogenic headache: a systematic review

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Sonal Goyal and Ajit Kumar are contributed equally and shared the corresponding authorship to this study.

**Efficacy of interventional treatment strategies for managing patients with cervicogenic headache: a systematic review**

경추성 두통환자에서의 중재적 시술 전략의 효능: 체계적 문헌고찰

경추성 두통(cervicogenic headache, CeH)은 경추 및 경추의 해부학적인 구조의 장애에 의해 유발된다. 보존적 치료에 반응하지 않는 환자들은 중재적 치료법을 받을 수 있다. 본 문헌고찰의 목적은 가용한 문헌들을 기반으로 다양한 중재 치료법을 기술하고 상대적 효능을 비교하는 것이다. 몇 가지 개별 중재 치료법에 초점을 맞춘 문헌고찰이 발표되었지만, 가용한 중재 치료법을 대상으로 한 문헌고찰과, 가장 효과적인 접근 방식을 확인하는 것은 여전히 필요하다. CeH의 치료를 위한 다양한 중재술에 관한 연구들에 대해 체계적 문헌고찰(PROSPERO: CRD42021246403)을 수행하였다. PubMed, Embase 및 Cochrane 데이터베이스를 이용하여 2001년 1월부터 2021년 3월 사이에 출판된 문헌들을 조사하였다. 두 명의 검토자가 포함된 연구에서 독립적으로 데이터를 추출하여 표로 요약하였다. 23건의 연구 중 11건은 CeH에서의 고주파 절제술(radiofrequency ablation, RFA)의 효과를, 5건은 후두 신경차단, 2건은 각각 후관절 주사와 심부 경부신경총 차단, 그리고 1건은 각각 환추(atlantoaxial, AA) 관절 주사, 경추 경막외 주사와 네 phé 신경마비(cryoneurolysis)를 평가하였다. RFA가 실험 using 2건의 연구를 제외하고 대부분의 연구에서 통증의 감소가 보고되었다. 가용한 문헌들에 의하면, 보존적 치료에 반응하지 않는 환자에서 후두신경차단, 경추 후관절 주사, AA 관절 주사, 심부 경부 신경총 차단, 경추 경막외 주사가 가능한 옵션일 수 있다. RFA는 장기적으로 좋은 결과를 보인 반면, 필수 치료는 더 안전한 치료법으로 알려졌다. 그러나 본 연구는 오직 제한된 근거급으로 발전하겠으므로 명확한 결과를 검증하기 위해서는 후속의 무작위 대조군 시험이 필요하다.

**Keywords**: Injections; Nerve block; Pain management; Radiofrequency ablation; Secondary headache disorders; Systematic review; Zygapophyseal joint.
Receiver operating characteristic curve: overview and practical use for clinicians
수신자 조작 특성: 개요와 임상의사를 위한 실제 활용법

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Statistical Round

https://doi.org/10.4097/kja.21209
pISSN 2005–6419 • eISSN 2005–7563

Received: May 18, 2021
Revised: July 9, 2021 (1st); August 19, 2021 (2nd)
Accepted: August 29, 2021

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진단 검사를 통하여 질병의 유무를 결정하는 것은 임상에서 중요한 과정이다. 많은 경우에서 진단 검사 결과는 연속형 값으로 얻어지게 되는 경우가 많기 때문에, 질병의 존재 유무를 판정하기 위해서는 연속형 결과값을 이분형으로 변화하고 질병의 유무를 판정하는 과정이 필요하다. 이 과정에서 주로 사용되는 방법은 receiver operating characteristic (ROC) 곡선이다. ROC 곡선은 진단 검사의 정반적인 성능을 평가하고, 두 개 이상의 진단 검사의 성능을 비교하는 데 사용된다. 또한, 질병 유무를 판단하기 위한 최적의 cut-off value를 선택하는 데에도 이용된다. 통계에 대한 전문 지식이 부족한 임상 의사는 ROC 곡선에 대한 복잡한 수학적 유도 및 분석 과정을 모두 이해할 필요는 없지만, ROC 곡선의 핵심 개념을 이해하는 것은 ROC 곡선을 제대로 이용하고 적절하게 해석하기 위한 전제 조건이다. 이 리뷰에서는 ROC 곡선의 올바른 사용 및 해석을 위하여 모수적/비모수적 ROC 곡선의 의미, ROC 곡선 아래 면적의 의미, 최적의 cut-off value를 선택하는 방법, ROC 곡선 분석을 위한 통계 프로그램에 대해서 기술한다.

Keywords: Area under curve; Mathematics; Reference values; Research design; ROC curve; Routine diagnostic tests; Statistics.

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Comparison of upper and lower body forced air blanket to prevent perioperative hypothermia in patients who underwent spinal surgery in prone position: a randomized controlled trial

Jae Hwa Yoo¹, Si Young Ok¹, Sang Ho Kim¹, Ji Won Chung¹, Sun Young Park¹, Mun Gyu Kim¹, Ho Bum Cho¹, Sang Hoon Song¹, Yun Jeong Choi¹, Hyun Ju Kim¹, Hong Chul Oh²

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Keywords: Body temperature; Forced-air warming; Hypothermia; Lower body; Prone position; Spine surgery; Upper body.
The impact of preoperative glycated hemoglobin (HbA1c) on postoperative complications after elective major abdominal surgery: a meta-analysis

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Keywords: Diabetes mellitus; Elective surgical procedures; General surgery; Glycated hemoglobin A; Operative surgical procedures; Postoperative complications.
Effect of postoperative non-steroidal anti-inflammatory drugs on anastomotic leakage after pancreaticoduodenectomy

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Keywords: Analgesics; Anastomotic leak; Non-steroidal anti-inflammatory agents; Pancreatic fistula; Pancreaticoduodenectomy; Postoperative complications.
Effects of dexamethasone on catheter-related bladder discomfort and emergence agitation: a prospective, randomized, controlled trial

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배경: 도뇨관 삽입에 따른 방광 불편감(catheter-related bladder discomfort, CRBD)은 도뇨관 삽입을 한 환자에서 흔하며, 각성홍분(emergence agitation, EA)의 위험 요인이다. CRBD 관리의 중심은 항콜린작용제이며, 택사메타손은 아세틸콜린의 분비를 저해한다. 본 연구는 수술 후 CRBD와 EA에 대한 택사메타손의 효과를 평가하는 데 목적으로 두었다.

방법: 이 전향적 연구에서는 도뇨관 삽입이 요구되는 비뇨기과 수술을 받은 90명의 환자들을 두 그룹 중 한 곳에 무작위로 배정하였다(각 n = 45). 마취를 유도하기 전 택사메타손군은 택사메타손 10 mg (2 ml)을 정맥으로 투여받았고, 반면에 대조군은 생리식염수 2 ml를 같은 방법으로 투여받았다. 일차 목적변수로서, CRBD의 발생률과 중증도는 환자가 마취 후 회복실(post-anesthesia care unit, PACU)에 도착한 후 0, 1, 2, 6시간 후에 평가되었다. EA의 발생률과 중증도는 이차 목적 변수로서 수술실에서 마취 후 각성 중과 PACU에서 회복 중에 비교 되었다.

결과: 수술 후 0, 1, 2, 6시간에 대조군과 택사메타손군에서 CRBD의 발생률은 각각 28.9%와 15.6%, 55.6%와 55.6%, 57.8%와 46.7%, 53.3%와 51.1%였다. 수술 후 0, 1, 2, 6시간에 평가된 CRBD의 발생률이나 중증도는 그룹 간 차이를 나타내지 않았다. 수술실과 PACU에서의 EA의 발생률과 중증도 역시 그룹 간에서 차이가 없었다.

결론: 마취 유도 전 택사메타손의 투어는 비뇨기과 수술을 받은 환자에서 CRBD 또는 EA의 발생률이나 중증도를 더 이상 감소시키지 않았다.

Keywords: Anesthesia; Catheters; Catheterization; Dexamethasone; Incidence; Urinary bladder.
Application of unilateral rhomboid intercostal and subserratus plane block for analgesia after laparoscopic cholecystectomy: a quasi-experimental study

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Keywords: Analgesia; Bupivacaine; Laparoscopic cholecystectomy; Nerve block; Pain; Pain management; Postoperative pain; Ultrasonography.

Received: May 30, 2021
Revised: July 12, 2021 (1st); July 16, 2021 (2nd)
Accepted: July 19, 2021

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배경: 복강경 담낭절제술 후 통증을 위한 편측 능형 늑간-거근하면 (RISS) 차단기법 적용: 준실험 연구

Application of unilateral rhomboid intercostal and subserratus plane block for analgesia after laparoscopic cholecystectomy: a quasi-experimental study

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배경: 복강경 수술 후 통증에 근막 사이 신경차단술(interfascial plane block)을 적용할 수 있다. 복강경 담낭절제술 후 초음파 유도 편측 능형 늑간-거근하면(unilateral rhomboid intercostal and subserratus plane, RISS) 차단기법이 진통제 사용량에 미치는 영향을 조사하는 것을 목표로 하였다.

방법: 복강경 담낭절제술을 받은 50명의 환자가 준실험 연구에 포함되었다. 포함기준을 충족 하는 환자는 실험군(20 ml 0.25% 부피바카인[bupivacaine] + 정맥내 환자 조절 진통제[IV-PCA] 트라마돌[tramadol])이 포함된 RISS 차단, n = 25) 및 대조군(IV-PCA 트라마돌, n = 25)의 두 그룹으로 나뉘어 분석되었다. 1차 분석결과는 24시간 동안 사용된 트라마돌의 총량이었다. 2차 분석결과는 NRS 점수에 따라 2, 6, 12, 24시간에 부작용, 추가 진통제 사용량 및 수술 후 통증(휴식 중 또는 활동 중)이 포함되었다.

결과: 수술 후 24시간의 트라마돌 사용량은 대조군보다 RISS군에서 유의하게 낮았다 (P < 0.001). 2시간과 6시간의 휴식 중 NRS 점수는 RISS군에서 통계적으로 유의하게 낮았다. RISS군의 활동 중 NRS 점수는 수술 후 2, 6 및 12시간에 유의하게 낮았다. 부작용 발생률과 추가 진통제 사용량에는 통계적으로 유의한 차이가 없었다(P > 0.05).

결론: 편측 RISS 차단은 복강경 담낭절제술 후 통증 관리에 효과적인 방법이며, 복합 진통의 일부로 사용할 수 있다.

Keywords: Analgesia; Bupivacaine; Laparoscopic cholecystectomy; Nerve block; Pain; Pain management; Postoperative pain; Ultrasonography.
Appropriately controlling acute postoperative pain is associated with improved recovery and postoperative outcomes. Postoperative pain should be controlled in the most effective and safest manner with the fewest side effects possible. Multimodal analgesia is a combination of various analgesics with different mechanisms of action that have additive or synergistic effects when taken together [1]. This allows for a lower total analgesic dose and fewer side effects, reducing the opioid requirement. Several drugs are currently used for multimodal treatment strategies, including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, gabapentinoids, N-methyl-D-aspartate receptor antagonists, glucocorticoids, lidocaine, alpha 2 agonists, and local anesthetics for regional blocks.

NSAIDs are effective non-opioid analgesics that are widely used in the perioperative setting. The primary mechanism of action is the inhibition of the cyclooxygenase (COX) enzyme, which blocks the inflammatory response by preventing the formation of prostaglandins. NSAIDs are categorized on the basis of their selectivity for COX-1 and COX-2. Non-selective NSAIDs block both enzymes, and the side effects of these drugs are mainly due to COX-1 inhibition, which is associated with a disturbance in vascular homeostasis [2].

The side effects of NSAIDs on renal function [3–6], cardiac events [7–9], perioperative bleeding [10–12], wound healing [13,14], and gastrointestinal events [15] have been assessed, with some concerning findings. However, the results are controversial and the evidence is not conclusive.

NSAIDs have been shown to have a strong analgesic effect similar to opioids [16–19], with similar acute postoperative pain control. This makes them suitable for reducing opioid consumption and thus improve bowel function [17,20]. However, safety concerns regarding postoperative anastomotic complications have recently been raised. Since NSAIDs can impair collagen deposition and angiogenesis, the strength of anastomosis is thus decreased [21,22]. Kotagal et al. [16], in their study of 398,752 patients undergoing gastrointestinal surgery, found that the administration of ketorolac was associated with an increased risk of readmission and reintervention due to anastomosis complications (odds ratio [OR]: 1.20, 95% CI [1.06, 1.36]). According to another large-scale retrospective cohort study, NSAIDs were found to increase the risk of anastomotic leaks (OR: 1.70, 95% CI [1.11, 2.68], P = 0.01) in patients undergoing bariatric or colorectal surgery [23].

Yoon et al. [24] retrospectively investigated the association between postoperative NSAID use and clinically relevant postoperative anastomotic leakage (postoperative pancreatic fistula [POPF] or hepatojejunostomy anastomotic leakage [HL]), in > 4,000 patients. The authors found a higher incidence of HL within the first 5 postoperative days in the group that received NSAIDs postoperatively (OR: 3.11, 95% CI [1.86, 5.21]). However, the overall incidence of HL was too low (1.9%) to allow for the role of NSAIDs to be analyzed as a risk factor for postoperative HL using binary logistic regression analysis. In addition, NSAID use was not a risk factor for POPF in that study [24].
Therefore, the question regarding whether NSAIDs should be used during pancreatic surgery remains unclear. There are numerous risk factors for postoperative anastomotic complications, including advanced age, large anastomotic tension, infection, neoadjuvant chemotherapy, co-existing inflammation for postoperative anastomotic complications, the use of vasopressors, and the skill of the surgeons. In addition, the cumulative dose of NSAIDs may be a more important risk factor than the use of NSAIDs [25]. To define the association between postoperative NSAID use and anastomotic complications and to find the optimal dose of NSAIDs, well-controlled and large-scale prospective studies are needed.

NSAIDs are central to the opioid-sparing multimodal analgesia technique. However, results have been inconclusive regarding the effect of early postoperative NSAID use and anastomotic leakage [25,26]. While NSAIDs can be safely used at an optimal dose and timing, a protocol for acute postoperative pain control should be established for postoperative NSAID use that involves a multidisciplinary discussion including both anesthesiologists and surgeons.

**Funding**

None.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**References**

Myocardial injury in noncardiac surgery

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Myocardial injury is defined as an elevation of cardiac troponin (cTn) levels with or without associated ischemic symptoms. Robust evidence suggests that myocardial injury increases postoperative mortality after noncardiac surgery. The diagnostic criteria for myocardial injury after noncardiac surgery (MINS) include an elevation of cTn levels within 30 d of surgery without evidence of non-ischemic etiology. The majority of cases of MINS do not present with ischemic symptoms and are caused by a mismatch in oxygen supply and demand. Predictive models for general cardiac risk stratification can be considered for MINS. Risk factors include comorbidities, anemia, glucose levels, and intraoperative blood pressure. Modifiable factors may help prevent MINS; however, further studies are needed. Recent guidelines recommend routine monitoring of cTn levels during the first 48 h post-operation in high-risk patients since MINS most often occurs in the first 3 days after surgery without symptoms. The use of cardiovascular drugs, such as aspirin, antihypertensives, and statins, has had beneficial effects in patients with MINS, and direct oral anticoagulants have been shown to reduce the mortality associated with MINS in a randomized controlled trial. Myocardial injury detected before noncardiac surgery was also found to be associated with postoperative mortality, though further studies are needed.

Keywords: Mortality; Patient outcome assessment; Postoperative complications; Postoperative period; Troponin I; Troponin T.

Introduction

The fourth universal definition of myocardial infarction distinguishes myocardial injury from myocardial infarction [1]. Myocardial injury is defined solely as the presence of at least one cardiac troponin (cTn) value above the 99th percentile upper reference limit (URL) of any assay and may or may not be associated with ischemic symptoms [1]. In 2012, a large international observational cohort study prospectively collected the postoperative cTn values of more than 40,000 patients from five continents and demonstrated a significant association between cTn values and postoperative mortality, without accounting for the presence of ischemic symptoms [2]. In a subsequent study, the study population was limited to those without ischemic features, and the significant association between myocardial injury and postoperative mortality was reproduced [3,4]. The incidence of postoperative myocardial injury in patients after noncardiac surgery is approximately 18%, making it one of the most common complications related to postoperative mortality, which is the main cause of death in developed countries [3,5]. In addition, more than 200 million patients undergo noncardiac surgeries annually worldwide [6,7]. Therefore, this review aims to provide a comprehensive examination of findings regarding myocardial injury in noncardiac surgery based on the characteristics of cTn levels, considerations of surgical patients, and the pathophysiology, diagnostic criteria, clinical...
consideration of postoperative myocardial injury in noncardiac surgery. We also briefly reviewed myocardial injury in the preoperative period since this has also been associated with postoperative outcomes [8–10].

Characteristics of cTn

Numerous cardio-specific markers have been proposed for the detection of myocardial damage. cTn is a component of the myofibrillar apparatus that was discovered in the 1960s, but it was not until the 1990s that a reliable serum assay was introduced [11]. There are three types of cTn (C, I, and T), each of which plays a different role in the contractile regulatory complex [12,13]. Specifically, cTn T binds to the actin filament, cTn C acts as a calcium ion binding site, and cTn I inhibits the interaction between actin and the myosin heads when the intracellular calcium concentration is insufficient to initiate muscle contraction. Additionally, cTn is present in skeletal muscle fibers; however, differences in the versions of cTn provide tissue specificity for cardiac muscle [14]. Compared to other cardiac markers, the advantage of cTn is that it performs better and has superior sensitivity [12,13]. Both cTn I and cTn T can be used to detect myocardial damage, with similar accuracy, as shown in a direct comparison between the recently available assays [15].

There are several challenges regarding the application of the cTn assay. The first is defining a normal cut-off limit. The 99th percentile URL is provided for each assay and is uniformly applied as a cut-off value. However, sex- and age-dependent differences in the 99th percentile URL have been reported [16]. Specifically, the rate of elevation in cTn levels increased considerably as the age limit of study patients was increased from those aged > 50 years to > 70 years [17,18]. In more recent studies, the prognostic relevance of cTn level elevation above the 99th percentile URL continued to be significant regardless of the sex and age of surgical patients [19,20]. The current recommendations suggest that the 99th percentile URL be used for any cTn assay that is available, but in the future, a different approach may be needed based on sex or age.

Another challenge is non-coronary causes of elevated cTn levels. Conditions that are not directly related to the heart can increase cTn levels. These include chronic kidney disease, sepsis, stroke, and cancer, among others [21]. Therefore, cTn levels have been more commonly used to rule out myocardial infarction in patients presenting with ischemic symptoms [22]. The following section describes what should be taken into account when interpreting cTn levels in surgical patients who do not have definite ischemic symptoms.

Considerations for surgical patients

The 99th percentile URL is provided by immunoassay manufacturers based on blood samples derived from apparently healthy individuals [23]. Compared with healthy individuals, surgical patients have higher risk conditions that may elevate cTn levels to different degrees. Some studies have argued that changes in cTn levels from pre- to post-operation need to be considered for surgical patients [18,23]. A specific threshold has been suggested for cTn T, namely, an increase in the peak level by at least 5 ng/L from the preoperative level of 20 ng/L [3]. A threshold of change has not been provided for the other assays, and the use of the 99th URL is still recommended.

Diagnostic criteria need to be limited to a common shared pathophysiology to explore prevention and treatment modalities. However, there are wide variations in the elevation of cTn levels in non-cardiac surgical patients, and the etiologies are not easily distinguishable. For instance, elevated cTn levels in chronic kidney disease are related to both a decrease in protein excretion and a higher possibility of concurrent myocardial damage [24,25]. The current diagnostic criteria for myocardial injury after noncardiac surgery (MINS) were proposed by the VISION (Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study) investigators. They excluded all cTn level elevations with a definite non-ischemic etiology. The following section of our review will be based on the diagnostic criteria of MINS and its clinical relevance.

Clinical relevance of MINS

The series of studies conducted by the VISION investigators have provided the most robust evidence for the clinical relevance of MINS [2,3,26]. The first insight came from the PeriOperative Ischemic Evaluation (POISE) trial. Most of the patients with postoperative myocardial infarctions in this trial did not have ischemic symptoms but still had postoperative outcomes [27]. The VISION investigators generated a cohort focusing on the association between postoperative cTn levels and mortality. The first report found that cTn levels were associated with postoperative mortality regardless of ischemic symptoms [2]. In the following studies, this association was maintained for high-sensitivity cTn T assays and for elevations in cTn levels during the first 30 days after surgery [3–5]. The presence of ischemic symptoms increased mortality by 55% in MINS patients. However, this increase was minor considering that the mortality rate in those who experienced MINS was nearly 8.5 times that of those who did not experience MINS [3,26].

Based on the VISION study findings, the following diagnostic
criteria for MINS were proposed: at least one postoperative cTn measurement above the 99th percentile URL within 30 days of surgery that was deemed a myocardial ischemic injury (i.e., supply-demand mismatch or thrombus) without evidence of non-ischemic etiology [3,26,28]. This includes both myocardial infarction and ischemic myocardial injury [3,26,28]. The clinical relevance of postoperative cTn level elevation has been validated in subtypes of noncardiac surgery, such as vascular surgery, lung surgery, and transplantation [29–33]. MINS showed prognostic relevance regardless of sex and age, although most of these studies, including the VISION cohort, recruited high-risk patients aged > 45 years [19,20].

Pathophysiology and incidence

Non-ischemic etiologies, such as rapid atrial fibrillation, sepsis, stroke, and pulmonary embolism, were reported in less than 15% of patients with cTn level elevations after noncardiac surgery [3,29]. The majority of the remaining cases that met the MINS criteria were found to be related to ischemic etiology. Of those with an ischemic etiology, the distribution of cases with oxygen supply-demand mismatch compared to those with thrombosis can be inferred from studies on postoperative myocardial infarction [34,35]. In the OPTIMUS trial, 30 patients with operative non-ST elevation myocardial infarction were compared with 30 patients with non-operative non-ST elevation myocardial infarction that were not related to the surgical procedure [34]. Cardiac catheterization with optical coherence tomography revealed that 67% of the non-operative myocardial infarctions had a thrombus, while only 13% of the perioperative myocardial infarctions were found to be associated with a thrombus. ST elevation myocardial infarctions, which were excluded from the OPTIMUS study, are almost always associated with thrombi [36]. Considering that ST elevation myocardial infarctions account for 10–20% of perioperative myocardial infarctions [27,37], 20–30% of patients with perioperative myocardial infarctions can be assumed to have a thrombus. Similar results were reported using coronary computed tomographic angiographic images of postoperative myocardial infarction, which revealed that 24% of the patients had coronary plaque [35]. While these studies only included patients with MINS who had ischemic symptoms, thrombus formation is not likely to be more common in patients who do not have ischemic symptoms. In a recent study, severe hypotension or anemia, which is known to induce an oxygen supply-demand mismatch, was associated with 72% of perioperative myocardial ischemic symptoms [38]. Taken together, about two-thirds to three-quarters of MINS are deemed to originate from an oxygen supply-demand mismatch, while thrombus formation contributes to a quarter or to a third at most.

Risk factors and prevention

Risk factors for MINS are consistent with perioperative myocardial infarctions, because they share a common pathophysiology. Predictive models for general cardiac risk stratification can be considered for MINS. These include old age, male sex, and comorbidities such as heart disease, cerebrovascular disease, diabetes, peripheral artery disease, aortic disease, and renal insufficiency [28]. Operative variables, which include the duration, type, and extent of the procedure, also contribute to the myocardial burden [39]. In addition, the exercise tolerance of patients and other cardiac maker measurements (such as brain natriuretic peptide) could be helpful in predicting risk [40–42].

Modifiable factors of MINS have been extensively evaluated. In the preoperative period, a low hemoglobin level was shown to be associated with the development of MINS [43,44]. However, the benefit of treating anemia remains controversial because transfusions could increase the myocardial burden and mortality of surgical patients [45,46]. Other treatment modalities for anemia may need to be investigated in relation to the occurrence of MINS. A sub-study of the VISION cohort demonstrated that a high preoperative blood glucose test was associated with MINS [47]. Similarly, a retrospective study also found that high preoperative glucose levels were associated with MINS; however, this study also found that preoperative hemoglobin A1c levels were not significantly associated [48]. This result suggests that immediate glucose control may still be crucial for preventing MINS, even in patients with poorly controlled glucose levels long-term [48].

The primary concern during anesthesia is maintaining an adequate blood pressure. A brief drop in blood pressure during surgical procedures is known to increase renal and myocardial injuries and mortality [49–52]. Specifically, MINS has been associated with an absolute mean arterial pressure < 65 mmHg and a relative decrease in the absolute mean arterial pressure > 30% from baseline [50]. Both the severity and duration of hypotension are key determinants [50]. However, hypotension seems to have less effect on MINS than other pre-existing factors, while the clinical implication of this association is that intraoperative blood pressure could be controlled with a large difference. Cardiac output-guided fluid therapy with low-dose inotropic drugs was evaluated in one study, but MINS occurrence was not significantly decreased [53]. Tachycardia is also known to induce myocardial infarction by increasing oxygen demand and causing insufficient diastolic filling time [54]. By enhancing the oxygen supply-de-
mand mismatch, the preoperative ambulatory heart rate has been associated with the development of MINS [55]. Adequate pain control has been reported to be associated with MINS; however, further investigation is needed [56,57].

Cardiovascular drug prescriptions can also be considered as a preventive for MINS. In the POISE trial, beta-blockers were associated with a decrease in postoperative myocardial infarctions but an increase in the incidence of stroke [38]. Thus, the use of beta-blockers immediately after surgery should be limited to those patients who already have routine prescriptions [59]. The use of other cardiovascular drugs, including aspirin, nitrous oxide, and clonidine, in the preoperative period was also investigated as a preventative for MINS, but the results were not significant [28].

Monitoring postoperative cTn

Ischemic symptoms in the perioperative period are likely to be masked by sedatives or confused with surgical pain [60]. The VI-SION cohort demonstrated that 40% of MINS occurred on the day of surgery, 40% on the first postoperative day, and 15% within 2 days after surgery [2,3,26]. However, without cTn monitoring, most of these myocardial injuries would likely go undetected, because more than 70% of patients with MINS do not present with any symptoms [3,26,29]. Therefore, routine postoperative cTn measurements may benefit patients with a certain amount of risk. Currently, recommendations suggest that cTn should be monitored in the perioperative period. Initially, the expert opinion was that screening should be conducted for patients aged > 45 years [61], and the following perioperative guidelines have also included various recommendations regarding cTn monitoring [62–64]. According to the guidelines of the American College of Cardiology/American Heart Association and the European Society of Cardiology/Anesthesiology, routine cTn screening is recommended for those with ischemic symptoms or those at high risk for cardiovascular events [62,63]. The most recent Canadian Cardiovascular Society guidelines made a stronger recommendation for cTn levels to be obtained daily for 2–3 days following surgery in patients with a cardiovascular risk > 5% based on the finding that the vast majority of clinically important MINS would otherwise go undetected [4,64].

Treatment

The only treatment that has been established by a large randomized trial of patients with MINS is the use of direct oral anticoagulants [65]. In the MANAGE trial, dabigatran 110 mg twice daily or placebo was prescribed to 877 patients in each group who were followed up for 16 months. Based on the incidence of major vascular complications, which was the primary outcome, the long-term continuous use of dabigatran was suggested for patients with acceptable bleeding risk. Life-threatening organ bleeding, which was the primary safety outcome, was not found to be increased by dabigatran. However, clinicians are generally concerned about the use of direct oral anticoagulants shortly after a surgical procedure, so there seems to be a dilemma in daily clinical practice. In addition, the benefit of using direct oral anticoagulants may appear contradictory since MINS is much more associated with oxygen supply-demand mismatch than with thrombus formation [34,35]. However, the direct oral anticoagulants are beneficial because the risk of thrombotic events is increased even in MINS caused by oxygen supply-demand mismatch [3,26]. In addition, the mortality associated with MINS is more frequently related to thrombus formation [3,26].

Observational studies have found other cardiovascular medical treatments to also be effective. An increase in the dose or early introduction of cardiovascular drugs, such as antiplatelets, statins, beta-blockers, and angiotensin-converting enzyme inhibitors have demonstrated improved outcomes in patients with MINS [66]. Aspirin was reported to be associated with a lower risk of 30-day mortality in a sub-study of the POISE trial [27]. Statins were associated with an improvement in long-term outcomes for patients who were discharged alive after experiencing MINS [67]. The benefit of statins for patients with MINS may not be limited to immediate lipid-lowering effects but may also be related to the pleuritic effect, because elevated C-reactive protein levels at discharge have been associated with mortality in this patient population [68]. Based on these findings, the use of low-dose aspirin and statins is recommended [64]. The two main types of renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), which are the drugs of choice for hypertensive patients with comorbidities, have also been found to be beneficial [69,70].

A proper evaluation of the coronary artery should be considered. Coronary angiographic or coronary computed tomographic angiographic images of perioperative myocardial infarctions frequently reveal a remarkable portion of extensive or complex coronary arteries that could benefit from coronary revascularization [71,72]. Conducting coronary angiographic evaluations has been associated with lower mortality from postoperative myocardial infarctions, with percutaneous coronary intervention being the most common modality for coronary revascularization [37]. However, only 21% of patients with perioperative myocardial infarctions and 8% of patients with MINS are evaluated using coronary angiography [29,37]. In fact, the risk and benefit of coronary
interventions should be taken into account more cautiously in patients who are at risk of bleeding shortly after surgery, because withdrawing antiplatelet therapy may lead to in-stent thrombosis [35]. Lastly, most of these procedures are performed in the cardiology department, and an evaluation by a cardiologist has been associated with improved outcomes in patients with MINS [73], though multidisciplinary management may also be helpful.

Myocardial injury in the preoperative period

As mentioned previously, cTn levels in surgical patients are frequently elevated even in the preoperative period. Chronic myocardial injury in the preoperative period was found to have a comparable effect on postoperative mortality with acute injury [10]. An increase in risk was also observed for minor elevations that did not exceed the 99th percentile URL [74]. In another observational study, the mortality risk was related to both the magnitude and timing of the peak cTn level [8]. While a higher preoperative cTn level was associated with higher postoperative mortality, a longer period of time between the peak level and surgery appeared to reduce this risk for mild elevations. Additionally, mortality was improved when myocardial injury was attenuated postoperatively [9]. However, since managing preoperative myocardial injury remains a clinical necessity, further investigations are needed to clarify these findings.

Conclusion

Myocardial injury, detected by cTn level elevations in the perioperative period of noncardiac surgery, is associated with adverse outcomes. A vast majority of patients with MINS do not have ischemic symptoms; therefore, routine monitoring of cTn may be beneficial during the first 48 h after surgery when MINS is most likely to occur. The use of dabigatran 110 mg twice daily has been reported to be effective in randomized controlled trials. Intensification of other cardiovascular drugs such as antiplatelets, antihypertensives, and statins has also been shown to improve outcomes after MINS.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Jungchan Park (Conceptualization; Project administration; Writing – original draft)
Jong-Hwan Lee (Supervision; Validation; Writing – review & editing)

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https://doi.org/10.4097/kja.21372


58. Poise Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G,


Cervicogenic headache (CeH) is caused by the disorder of the cervical spine and its anatomical structures. Patients who fail to respond to conservative therapies can undergo interventional treatment. The purpose of this review is to describe the various interventions and compare their relative efficacies. Although a few reviews have been published focusing on individual interventions, reviewing studies on other available treatments and establishing the most efficacious approach is still necessary. We performed a systematic review of studies available on the various interventions for CeH. The PubMed, Embase, and Cochrane databases were searched for literature published between January 2001 and March 2021. Based on the inclusion criteria, 23 articles were included. Two reviewers independently extracted the data from the studies and summarized them in a table. Eleven of twenty-three studies evaluated the effect of radiofrequency ablation (RFA), 5 evaluated occipital nerve blocks, 2 each for facet joint injections and deep cervical plexus blocks, and 1 study each evaluated atlantoaxial (AA) joint injections, cervical epidural injection, and cryoneurolysis. Most of the studies reported pain reduction except 2 studies on RFA. In conclusion, based on the available literature, occipital nerve blocks, cervical facet joint injection, AA joint injection, deep cervical plexus block, and cervical epidural injection may be reasonable options in refractory cases of CeH. RFA was found to have favorable long-term outcomes, while better safety has been reported with pulsed therapy. However, our review revealed only limited evidence, and more randomized controlled trials are needed to provide more conclusive evidence.

Keywords: Injections; Nerve block; Pain management; Radiofrequency ablation; Secondary headache disorders; Systematic review; Zygapophyseal joint.

Introduction

Cervicogenic headache (CeH) is a secondary headache characterized by unilateral pain that is caused by a disorder of the cervical spine and its anatomical structures, mainly innervated by the C1, C2, and C3 spinal nerves [1]. It was first described in 1983 by Sjaastad et al. [2]. Due to its significant overlap with migraine and a lack of easily applicable tests and diagnostic criteria, CeH is difficult to diagnose and treat [3]. The diagnostic criteria for CeH have been revised and modified in the third edition (beta version) of the International Classification of Headache Disorders (11.2. Headache attributed to neck disorders: 11.2.1 CeH) [4]. The prevalence of CeH ranges from 1% to 4.1% in the general population, with no clear male or female predominance [5].

The pathogenesis of CeH is due to the convergence of nociceptive afferents from the
upper three cervical nerves and trigeminal nerves onto the second-order neurons in the trigeminocervical nucleus in the upper cervical spinal cord (C1–C3). Therefore, every cervical structure innervated by the trigeminocervical caudalis nucleus (joint, muscles, nerves, ligaments, and dura) is implicated in the genesis of Cervicogenic Headache (CeH) [6]. The patient’s history and physical examination are the most useful tools for diagnosing CeH. Additionally, diagnostic zygapophyseal joint injections and cervical nerve and medial branch blocks can be used to confirm the diagnosis and predict treatment efficacy [7]. Owing to its complex etiology, a multidisciplinary treatment approach must be utilized. Currently, there is limited literature available regarding the effectiveness of pharmacological drugs and physical therapy, such as muscle stretching and manual cervical traction [8]. When conservative treatment fails, interventional pain management strategies can be used. This includes greater occipital nerve (GON) and lesser occipital nerve (LON) blocks, cervical spinal rami blocks (C1–C3), medial branch of C3, C4 dorsal rami blocks, intraarticular zygapophyseal joint (C2–C3, C3–C4) injections, atlantoaxial (AA) joint injections, cervical epidural steroid injections, radiofrequency ablations (RFAs), and occipital nerve stimulation [8,9]. Surgical interventions are also an option; however, these are often considered a last resort because of their ineffectiveness and high associated risk of complications [7]. In contrast to other secondary headaches, CeH does not improve over time [10]; therefore, finding an effective treatment is highly clinically important. Previously published reviews have mainly focused on individual interventions rather than summarizing all available interventions for managing CeH [11–13]. Therefore, an analysis and interpretation of the other available treatment modalities is warranted. The purpose of this review was to determine the various therapeutic interventions available and to make a comparative evaluation to establish the most efficacious approach for the management of CeH.

Materials and Methods

Study design

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). A prior protocol for this review was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO, no. CRD 42021246403).

Literature search strategy

An electronic search of the PubMed, Embase, and Cochrane databases for studies published between January 2001 and March 2021 was performed. The search terms “cervicogenic headache,” “secondary headache,” “interventions,” “nerve blocks,” “occipital nerve block,” “zygapophyseal joint injection,” “median branch block,” “pulsed radiofrequency,” and “radiofrequency neurotomy” were combined in different ways to search the databases. Two independent researchers searched the available literature and collected all the relevant articles. All the selected abstracts were reviewed by another researcher. A well-drafted PICOS framework was used to conduct the study (Table 1).

After the electronic databases were searched and the duplicates were removed, 6,484 articles were retrieved. Articles in languages other than English, animal studies, and abstract-only articles were not included. We also excluded literature reviews, systematic reviews, editorials, case reports, case series, non-scientific commentaries, reports, and news articles from this analysis. The full text of the article was obtained if the title or abstract discussed interventions for CeH management. If there were other pathologies, such as cranial masses, head injury, or any intracranial surgeries, the article was excluded. A total of 130 full-text articles were reviewed for eligibility. The references of the selected articles were also searched for additional studies matching the inclusion criteria. A total of 23 articles were included in the final analysis (Fig. 1).

Table 1. PICOS Framework

| Population | Age: adults > 18 years  
| Diagnostic: patients with CeH unresponsive to conservative therapy |
| Interventions | Various interventional approaches for CeH management:  
| • GON and LON block  
| • Facet joint intraarticular injection  
| • Lateral atlantoaxial intraarticular injection  
| • Deep cervical plexus block  
| • Cervical epidural steroid injection  
| • Radiofrequency ablation  
| • Cryoneurolysis |
| Controls | Varies from study to study, compared to control groups and/or placebo group |
| Outcomes | Primary objective  
| • Reduction of pain scores (NRS or VAS)  
| Secondary objective  
| • Duration of pain relief  
| • Effect on quality of life  
| • Adverse effects |
| Study design | Prospective randomized and non-randomized controlled trials, cohort studies, retrospective studies |

Assessment of risk of bias in individual studies

The methodological quality of the included studies was assessed using the “risk of bias” of the Review Manager Software version 5.4 (The Cochrane 14 Collaboration, UK). Two authors independently assessed the quality of each study, and disagreements were resolved through discussion. Seven categories, which included random sequence generation and allocation concealment to detect selection bias, blinding of the participants for performance bias, blinding of the outcome assessor for detection bias, incomplete outcome data for attrition bias, selective reporting for reporting bias, and other bias, were rated as “high,” “low,” or “unclear” to assess the internal validity of each study (Figs. 2 and 3).

Data extraction

The 23 included articles were fully reviewed by two reviewers who independently extracted and summarized the data in a table under the following headings: 1) author name, 2) year of publication, 3) type of study, 4) population, 5) intervention(s), 6) results, and 7) conclusion. Due to the lack of homogenous data and high-quality randomized controlled trials, only a systematic review could be performed.

Results

Therapeutic interventions for the treatment of CeH that were included in this systematic review included occipital nerve blocks (GON and LON blocks), facet joint intraarticular injections, lateral AA joint intraarticular injections, deep cervical plexus blocks, cervical epidural steroid injections, RFAs, and cryoneurolysis. Of the twenty-three included studies, eleven evaluated the effect of RFA on CeH, five evaluated the role of occipital nerve blocks (GON, LON), two evaluated facet joint injections, two evaluated deep cervical plexus blocks, and one study each evaluated AA joint injections, continuous cervical epidural injections, and cryoneurolysis (Fig. 4). Data from the included studies are summarized in Table 2.

The efficacy of occipital nerve blocks (GON, LON) in CeH treatment was evaluated by randomized controlled trials by Inan

Fig. 1. PRISMA flow diagram.

Fig. 2. Risk of bias graph. Review authors’ judgements about each risk of bias item presented as percentages across all included studies.

https://doi.org/10.4097/kja.21328
et al. [14], Naja et al. [9], Lauretti et al. [15] and found significant decrease in pain scores and rescue analgesics consumption in nerve block group. Another non-controlled prospective trial by Pingree et al. [16] reported significant pain reduction following GON block at C2 level and a retrospective review by Ertem and Yilmaz [17] described the successful role of repeated GON blocks in refractory cases of CeH.

Retrospective studies by Slipman et al. [18] and Zhou et al. [19] evaluated the role of facet joint injection in the treatment of CeH emanating from upper cervical facet joints. Zhou et al. demonstrated significant decrease in pain score after C1–C2, C2–C3 facet joint injection along with C2, C3 spinal rami block. Narouze and Provenzano [20] showed significant pain reduction following lateral AA joint injection in CeH patients showing AA joint involvement.

A randomized controlled study by Goldberg et al. [21] and non-randomized study by Wan et al. [22] demonstrated effective pain relief following deep cervical plexus block. A retrospective study by He et al. [23] showed significant pain reduction following continuous cervical epidural block for at least 6 months in CeH patients.

**Fig. 3.** Risk of bias summary. Review authors’ judgements about each risk of bias item for each included study.
<table>
<thead>
<tr>
<th>Article (yr)</th>
<th>Study type</th>
<th>Participants</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inan et al. 2001 [14]</td>
<td>Randomized prospective comparative study</td>
<td>28 patients with CeH based on diagnostic criteria by Sjaastad et al.</td>
<td>GON block group and C2/C3 nerve block group (1% lidocaine diagnostic block followed by two weekly injections of 0.25% bupivacaine)</td>
<td>Decreased pain frequency/duration in both groups lasting at least 2 months, with no significant group differences except pain frequency in first week after first therapeutic block (significantly lower in C2/C3 group)</td>
<td>Both blocks are equally effective for diagnosis and treatment of CeH</td>
</tr>
<tr>
<td>Naja et al. 2006 [9]</td>
<td>Double blind, placebo controlled</td>
<td>50 (25 target, 25 control) patients with CeH</td>
<td>GON and LON blocks with or without facial nerve block (16/25); anesthetic block group compared with placebo group</td>
<td>Significant pain improvement, decreased analgesic use, and decreased duration/frequency of headache at 2 weeks</td>
<td>Nerve stimulator-guided occipital nerve block provides relief of pain and accompanying symptoms for up to 2 weeks</td>
</tr>
<tr>
<td>Lauretti et al. 2014 [15]</td>
<td>Randomized double-blinded</td>
<td>30 patients with unilateral cervical pain with most painful point located on ipsilateral GON</td>
<td>GON block performed using classic technique followed by sub-compartmental technique if VAS &gt; 3; final volume of 5, 10, or 15 ml (10 mg dexamethasone + 40 mg lidocaine + nonionic iodine contrast + saline)</td>
<td>Significant decrease in VAS and rescue analgesic consumption in all subcompartmental groups lasting 24 weeks compared to only 2 weeks for classic technique</td>
<td>-Classic technique resulted in only 2 weeks of analgesia whereas sub-compartmental resulted in at least 24 weeks of analgesia; -5 ml volume sufficient for successful block</td>
</tr>
<tr>
<td>Pingree et al. 2017 [16]</td>
<td>Prospective open label</td>
<td>14 patients with occipital neuralgia or CeH</td>
<td>US-guided GON block at C2 level, 4 ml [1 ml of 2% lidocaine + 2.5 ml of 0.25% bupivacaine + 3 mg betamethasone] injected</td>
<td>Successful block in 86% of patients. Significant decrease in mean NRS from 4.71 (baseline) to 3.78 at 30 minutes, 2.64 at 2 weeks, and 2.21 at 4 weeks</td>
<td>Successful blockade of GON at C2 using US-guided technique -Significant reduction in pain scores observed over 4-week period -No significant adverse effects reported</td>
</tr>
<tr>
<td>Ertem and Yılmaz, 2019 [17]</td>
<td>Retrospective cohort study</td>
<td>21 patients with CeH who underwent at least 3 GON blocks, attended at least 3 follow-up appointments, and were admitted to the headache clinic during a 6-month period</td>
<td>GON block at the scalp; injection mixture of 3-4 ml of 2% lidocaine + 1 ml methylprednisolone</td>
<td>Significant decline in mean NRS by first month (second injection), second month (third injection), and third month (fourth injection) -8 patients reported no pain after the second injection and thus did not receive a fourth injection</td>
<td>Repeat GON injections is an effective option in patients not responding to conservative therapy -No serious complication was noted</td>
</tr>
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Cervical facet joint injections

Slipman et al. 2001 [18] Retrospective
- 18 patients with unremitting daily headaches after flexion/extension injury of upper cervical spine with tender facet joint not responding to conservative therapy
- Symptom duration ~34 months
- C2–C3 facet joint diagnostic block followed by therapeutic injection if decrease in VAS was > 80%
- If symptom relief was < 90%, second therapeutic injection given after 2 weeks
- Follow up at ~19 months
- Average decrease in VAS (from 8.2 to 5.5)
- 50% of patients experienced headache < 3 times/month, and 61% experienced < 3 episodes/week responsive to oral analgesics

Intraarticular facet joint injection is effective for treating headaches emanating from the C2–C3 joint after whiplash event

Zhou et al. 2010 [19] Retrospective observational
- 31 patients who failed multiple pharmacological/other treatments
- C1/2, C2/3 facet joint block and C2 and C3 spinal rami blocks using 0.5 ml 0.25% bupivacaine + 3 mg betamethasone
- > 50% headache relief in 90.3% (28) of patients immediately after procedure; however, 9.7% (3) of patients did not respond
- C1/C2 and C2/C3 facet joint and spinal rami blocks provide significant prolonged pain relief in > 90% of patients

AA joint intraarticular injection

Narouze and Provenzano, 2007 [20]
- 32 patients with clinical picture suggestive of AA joint pain, intractable headaches, and failed multiple drug treatment
- Classic intraarticular posterior approach, lateral AA joint injection (1 ml bupivacaine 0.5% + 10 mg triamcinolone)
- Post-procedure pain score was 0 in 46.8% of patients (15); ≥ 50% decrease in pain score in 81.2% of patients (23)
- Significant decrease in pain score at 1 and 3 months but not at 6 months
- Lateral AA intraarticular steroid injections provide short-term analgesia

Deep cervical plexus block

Goldberg et al. 2008 Prospective
- 39 patients with CeH
- Deep cervical plexus block @ C2/C3 using 10 ml 0.25% bupivacaine + 80 mg methylprednisolone
- For unilateral headache, unilateral block given and repeated on contralateral side after 1 week for global headache
- Pain assessed pre- and immediate post-injection and at 3 and 6 months
- Significant decrease in pain scores (P < 0.001)
- 33% of patients reported pain scores ≤ 4 after their last treatment
- 24% (10) had pain scores ≤ 4 at 3 months and 18% (7) had pain scores ≤ 4 at 6 months
- Significant decrease in pain after initial as well as last treatment
- For some patients, effective pain relief was seen for 3 months but by 6 months, pain had returned to pre-treatment levels
- US-guided approach showed similar satisfactory effect as FL-guided with advantage of no radiation exposure

Wan et al. 2017 [22] RCT; single-blinded
- 56 patients with CeH randomly recruited to either US-guided or FL-guided injection group
- Mixture of 2–4 ml 1% lidocaine + 7 mg betamethasone injected along C2 and/or C3 transverse process
- Significant decrease in NRS in both groups (P < 0.05) at 2, 12, and 24 weeks post-injection
- No serious side effects reported
- DCP block provides significant pain relief (for up to 6 months)
- US-guided approach showed similar satisfactory effect as FL-guided with advantage of no radiation exposure

(Korean J Anesthesiol 2022;75(1):12-24)
<table>
<thead>
<tr>
<th>Continuous cervical epidural block</th>
<th>He et al. 2009 [23]</th>
<th>Retrospective observational</th>
<th>37 patients with CeH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural catheter placed in C6–C7, C7–T1 or T1–T2 space; lidocaine (100–200 mg) + dext. (1–2 mg) + saline (total 250 ml) infused @ 5 ml/hr for 3–4 weeks. In addition, 5 mg triamcinolone given once weekly for 3–4 weeks; then catheters removed</td>
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<td>Days with mild/moderate pain, occurrence of severe pain, and daily NSAID dose (mg) significantly reduced 6 months after catheter placement compared to 3 months prior to procedure</td>
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<td>Effective for at least six months.</td>
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<td>Further research is needed to elucidate mechanisms of action and to prolong this effect</td>
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<tr>
<th>Radiofrequency ablation (RFA)</th>
<th>Stovner et al. 2004 [25]</th>
<th>Randomized, double-blind</th>
<th>12 patients with refractory CeH randomized into RFN of C2–C6 facet joints vs. sham treatment</th>
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<tbody>
<tr>
<td>RFA of medial branch of C2–C6 facet joints on the symptomatic side</td>
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<td>Slight improvement was at 3 months in RFN group, but no significant difference was seen after 3 months</td>
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<tr>
<td>No benefit with the procedure</td>
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<tr>
<td>Minor and short-term side-effects were seen</td>
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| Haesleragl et al. 2006 [26] | Randomized, controlled | 30 patients with CeH randomized into two groups, the RFA group (n = 15) and the LA group (n = 15) |
|-----------------------------|--------------------------|--------------------------|--------------------------|
| RFA of medial branches of dorsal rami of C3–C4 facet joint vs. LA with steroid injection at GON, followed by TENS when necessary |
| No statistically significant differences in pain scores |
| No evidence that RFN of cervical facet joints is a better treatment than infiltration of GON followed by TENS |

| Govind et al. 2003 [27] | Prospective, non-randomized | 49 patients suffering from third occipital nerve headache |
|-------------------------|-----------------------------|--------------------------|--------------------------|
| RFN of third occipital nerve (medial branch of C3 spinal nerve, supplying C2–C3 facet joint) |
| 88% achieved a successful outcome |
| Median duration of relief was about 297 days |
| Significantly reduced headache severity in 73% of patients at 12 months |
| 75% pain relief seen in majority of patients |
| Reduced analgesic intake by 70% |
| Average headache episode decreased from 6.2 to 2.8 days/week |

| Lee et al. 2007 [28] | Prospective observational | 30 patients suffering from chronic CeH for > 6 months, with > 50% pain relief from two diagnostic C3–C4 cervical medial branch blocks |
|----------------------|--------------------------|--------------------------|--------------------------|
| RFN of medial branch of C3–C4 facet joint |
| VAS score decreased by around 60% at 6 months |
| No serious complication was reported |

| Park et al. 2011 [29] | Retrospective observational | 11 patients with CeH |
|-----------------------|--------------------------|---------------------|--------------------------|
| RFN of lower cervical medial branches (C4–C7) |
| VAS score decreased by around 60% at 6 months |
| No serious complication was reported |

| Gahreleik et al. 2011 [30] | Randomized clinical pilot study | 30 patients with refractory CeH randomized into two groups: the LA group (n = 15) and the PRF group (n = 15) |
|---------------------------|-----------------------------|--------------------------|--------------------------|
| GON block with LA and steroid compared to PRF of GON |
| Significant decrease in VAS seen in both groups at 3 months |
| at 9 months, greater pain relief in PRF group than LA group |
| PRF provides greater long-term pain control |
| No complications reported |

(Continued to the next page)
Halim et al. 2010
Retrospective study
86 patients with CeH
Lateral C1–C2 joint PRF using intra-articular anterolateral approach
RFA of C2 DRG
Roughly 50% of patients had > 50% pain relief at 2 and 6 months and 1 year
PRF of lateral C1–C2 joints is feasible in refractory cases of CeH

Hamer and Purath, 2014 [32]
Retrospective observational
40 patients with refractory CeH and/or occipital neuralgia
RFN of C2 DRG and/or third occipital nerve
-35% of patients reported complete pain relief
-70% reported ≥ 80% pain relief
-86.5% of patients reported pain relief lasting for 25.4 weeks
-Repeat RFA showed similar result to first RFA in 59% of patients
-32% reported repeat RFA was more effective
RFN of C2 DRG and/or third occipital nerve can provide > 50% pain relief
-Repeat RFA is a feasible option for recurrent cases
-Effectiveness of repeat RFA is the same or better than the first RFA
-High likelihood of side effects but well-tolerated

Hamer and Purath, 2016 [33]
Retrospective observational
23 patients with recurrent CeH or occipital neuralgia
Repeat RFA of C2 DRG and/or third occipital nerve
-86.5% of patients reported pain relief lasting for 25.4 weeks
-Repeat RFA is a feasible option for recurrent cases
-Effectiveness of repeat RFA is the same or better than the first RFA
-High likelihood of side effects but well-tolerated

Li and Feng, 2019 [34]
Case control
139 patients with CeH, 87 in the PRF + ESI group and 52 in the ESI only group
PRF for C2 DRG and ESI
-Median pain relief was 4 months for the ESI group and 8 months for the PRF + ESI group
-No serious adverse effects reported
Combination of PRF C2 DRG + ESI is relatively safe, provides sustained pain relief, and improves quality of life

Lee et al. 2020 [35]
Retrospective observational
Electronic medical records of 45 patients with CeH (initially 114 patients recruited, 45 of which underwent PRF of C2 DRG)
C2 DRG PRF after recurrence of CeH following initial relief 24 hrs after diagnostic C2 DRG block
-40% of patients (18/45, success group) ≥ 50% pain relief after 6 months
-No post-procedure complications reported
C2 DRG PRF effective treatment for CeH, especially for those with positive C2 DRG diagnostic block

Cryoneurolysis
Kvarstein et al. 2019 [36]
RCT, double-blind
52 patients with unilateral CeH not responding to conservative treatment
After positive diagnostic block, 52 patients were randomly allocated to two groups (3:2): the occipital cryoneurolysis (31) group and the injection group (21) [1 ml depo-medrol (40 mg/ml) + 1 ml bupivacaine (5 mg/ml)]
-Significant reduction in pain > 50% and number of people consuming opioids in both groups
-No significant difference seen between groups
-Various transient/minor side effects reported but no significant group differences seen
Cryoneurolysis provides substantial but temporary pain relief, and the effect was not significantly different from the injection group

Interventions for cervicogenic headache

RFA is a promising approach that provides sustained pain relief. Pulsed radiofrequency (PRF) is considered a more satisfactory alternative to conventional RFA since it is associated with a better safety profile and fewer complications [24]. High-voltage radiofrequency pulses induce an inhibitory electric field around nociceptive fibers and disrupt pain transmission. Of the 11 included studies on the efficacy of RFA, three were RCTs, two were prospective, and six were retrospective. RFA targeting the medial branches supplying the cervical facet joints have been evaluated by Stovner et al. [25], Haspeslagh et al. [26] and demonstrated no benefit. Non-randomized studies by Govind et al. [27] and Lee et al. [28] showed significant headache relief after positive diagnostic block. Park et al. [29] demonstrated the role of lower cervical disorders in CeH genesis which could be improved by RFA of involved medial branches. PRF of GON was evaluated by Gabrhelik et al. [30] in a randomized study and reported long lasting significant pain relief in PRF group. PRF of lateral C1–C2 joint was evaluated by Halim et al. [31] and reported >50% pain relief in approximately 50% of the patients over 1 year follow-up period. Hamer and Purath [32] demonstrated >50% pain relief following RFA of C2 dorsal root ganglion (DRG) and in another study, also reported that efficacy of repeat RFA is usually same or better than first ablation in recurrent cases of CeH [33]. Efficacy of C2 DRG PRF combined with epidural steroid injection (ESI) was evaluated by Li and Feng [34] and reported significant pain relief with median relief of 8 months in PRF+ESI group. Another study by Lee et al. [35] also demonstrated significant pain relief following PRF of C2 DRG in patients who showed positive C2 DRG diagnostic block.

Cold temperature mediated ablation of sensory nerve fibers is relatively safe neuroablative technique. Cryoneurolysis of GON and LON was evaluated in refractory cases of CeH after positive diagnostic block in a randomized study by Kvarstein et al. [36] and found significant pain reduction in both the treatment groups with no significant group difference.

Discussion

CeH is a clinical syndrome with various presentations and multiple pain generators that involves cervical structures, mainly the upper cervical spinal nerves; C2–C3, C3–C4 facet joints; AA joints; C2–C3/C3–C4 intervertebral discs; atlantooccipital joints; GONs; and LONs [37]. Given the limited role of conservative management, this systematic review aimed to ascertain the efficacy of these different interventional approaches in the management of CeH.

Occipital nerve blocks (GON, LON)

Due to the convergence of the upper cervical and trigeminal sensory pathways, the bidirectional referral of nociceptive sensations between the neck and trigeminal receptive fields of the head and face leads to the referral of CeH pain from a cervical source to the forehead, temple, or orbit [6]. This forms the background for managing CeH through blocking the GON. Anesthetic blocks of the LON and facial nerve have also been found to be effective [9]. Inan et al. [14] compared the effect of GON blocks to C2/C3 spinal rami blocks in 28 patients with CeH and concluded that both blocks are equally effective. No significant difference was observed between the two groups in terms of pain frequency or degree of pain, except for pain frequency in the first week following the first therapeutic block, which was significantly reduced in the C2/C3 group. Another study by Naja et al. [9] evaluated 50 patients with CeH who received GON and LON blocks with or without facial nerve blocks. The anesthetic block group, which received a mixture of lidocaine, bupivacaine, epinephrine, fentanyl, and clonidine, was compared with the placebo group (normal saline) and a statistically significant improvement in pain intensity, frequency, and duration as well as a decrease in analgesic use were observed at 2 weeks in the block group compared to the placebo group. Lauretti et al. [15] evaluated 30 patients with unilateral CeH who underwent GON blocks using the classic technique (1 cm below the level of the superior nuchal line, just medial to the pulsation of the occipital artery). The visual analog scale (VAS), which is a tool used to evaluate pain using a 10 cm line with no marking that ranges from no pain (0) to worst possible pain (10), was used. Those with a score > 3 were randomly allocated into 3 groups (n = 10) who underwent GON blocks with 5, 10, or 15 ml of volume using the suboccipital compartmental technique. A significant decrease in the pain score and rescue analgesic consumption and an improved quality of life were seen in all subcompartmental groups for 24 weeks compared to only 2 weeks with the classic technique. Pingree et al. [16] evaluated 14 patients who underwent ultrasound-guided GON blocks at the C2 level and reported a successful block in 86% of patients 30 min post-injection. A significant decrease in the mean numerical rating scale (NRS) score, which is an 11-point scale ranging from 0 “no pain” to 10 “worst pain,” was observed at 30 minutes, 2 weeks, and 4 weeks compared to baseline. Although the sample size was very small, a significant reduction in the pain score was observed. Ertem and Yilmaz [17] retrospectively evaluated 21 patients with CeH who underwent at least three GON blocks and attended at least three follow-up appointments. A significant reduction in pain scores was seen at 3 months post-treatment. Some other previous studies
found an overall pain reduction of more than 50% [14–17] or nearly 50% [9] in the mean NRS or VAS score following occipital nerve blocks to treat CeH, with a short duration of pain relief usually lasting for a few weeks [9,14–16]. Repeat injections may be effective for sustained pain relief [17].

Facet joint injections

The beneficial effect of facet joint injections for the treatment of CeH has been reported in a few studies. Slipman et al. [18] reviewed 18 patients with unremitting headaches after flexion/extension injuries associated with tenderness over the upper cervical zygapophyseal joint who underwent a C2–C3 zygapophysial joint injection. A second injection was administered after 2 weeks if pain relief was < 90%. Although the average decrease in the VAS score (from 8.2 pre-injection to 5.5 post-injection) was not significant, the headache frequency, response to analgesics, and employment status improved significantly. Another retrospective chart review of 31 patients with refractory CeH who underwent C1–C2 and C2–C3 facet joint injections and C2 and C3 spinal rami blocks was conducted by Zhou et al. [19]. In that study, 28 patients showed a > 50% reduction in pain for an average duration of 21.7 days. A significant decrease in the mean pain intensity was observed immediately after injection. The study outcomes suggested that C1–C2, C2–C3 facet joint dysfunction and subsequent irritation of the spinal rami at C2 or C3 may contribute to CeH development and that steroid injections reduce spinal nerve root irritation and thus improve CeH. Despite the small sample size in the above two studies, the suggested contribution of upper cervical arthropathy in the generation of CeH and the effectiveness of both cervical facet joint injections and C2–C3 spinal rami blocks for pain relief were notable. No treatment-related complications were observed.

AA joint intraarticular injection

Narouze and Provenzano [20] conducted a retrospective chart review of 32 patients with CeH suggestive of AA joint pain who underwent AA joint intraarticular injections. Complete pain relief was observed in 15 patients, and 23 patients experienced a ≥ 50% reduction in pain. The mean pain score decreased significantly from pre-procedure to immediate post-procedure and at 1 month and 3 months, but not at 6 months. Therefore, this study showed the short-term pain relief provided by intraarticular AA steroid injections. However, there was not sufficient data to determine its long-term effects.

Deep cervical plexus block

A deep cervical plexus block can be useful for refractory cases of CeH, as pain often occurs over the C2 or C3 spinal nerve root distribution. Goldberg et al. [21] demonstrated a significant reduction in pain scores immediately after receiving a deep cervical plexus block at the C2/C3 level in 39 patients with CeH. While some patients experienced effective pain relief for 3 months, pain scores had returned to baseline levels by 6 months. The injection effectiveness was rated at 42% effective for all first injections and 40% effective for the last injection. Wan et al. [22] evaluated 56 patients who underwent either an ultrasound-guided or fluoroscopic-guided deep cervical plexus block along the C2 and/or C3 transverse process and reported a significant decrease in pain intensity (NRS) in both groups at 2, 12, and 24 weeks post-injection, with no significant differences observed between the groups. However, the small sample size and lack of double-blinding limited the strength of these findings and a clear understanding of the role of this treatment for CeH management [21,22].

Continuous cervical epidural block

He et al. [23] evaluated 37 patients with CeH treated with continuous cervical epidural block using lidocaine, dexamethasone, and saline (5 ml/h) for 3–4 weeks and triamcinolone 5 mg once a week for 3–4 weeks, and found it to be effective for at least 6 months. However, further research is needed to elucidate the mechanism and validate this outcome.

Radiofrequency ablation

For CeH patients who fail the interventions mentioned above or for those with severe or refractory CeH, radiofrequency lesioning may be an option. The targeted pain generators are the facet joint and its nerve supply (medial branch of the spinal dorsal rami), the third occipital nerve (branch of the dorsal rami of the C3 spinal nerve, supplying the C2–C3 facet joint), the GON, lateral C1–C2 joint, and C2 DRG.

Stovner et al. [25] evaluated RFA of the medial branch of the C2–C6 facet joints ipsilateral to the pain in 12 patients and compared them to those receiving sham treatment. A slight improvement was noted at 3 months, but after this time and over a duration of 2 years, no statistically significant differences were observed. Haspeslagh et al. [26] evaluated 15 patients who received RFA of the C3–C6 facet joints and the DRG and compared them with a local anesthetic block of the GON. No statistically significant difference in pain scores was seen, suggesting that RFA of the

https://doi.org/10.4097/kja.21328
cervical facet joint was no better at reducing pain than local infiltration of the GON. Therefore, both of the above studies showed that RFA provided no significant benefit.

Govind et al. [27] described the effect of RFA of the third occipital nerve for the treatment of referred pain from C2–C3 facet joints in 49 patients and reported successful outcomes in 88% of the patients with pain-free intervals lasting for approximately 297 days. Fourteen patients underwent repeated procedures, 86% of which (12 patients) experienced pain relief for the next 217 days. The study concluded that third occipital nerve RFA was effective for pain relief and repeat ablations can prolong its efficacy. Lee et al. [28] evaluated 30 patients with CeH who underwent RF neurotomy of the cervical facet joints after positive diagnostic blocks and found substantial pain relief over a 12-month follow-up period. Another study by Park et al. [29] evaluated 11 patients with CeH who underwent RFA of the medial branches of the lower cervical nerves (C4–C7) and reported a significant decrease in VAS scores at 6 months (from 8.1 ± 1.1 to 2.7 ± 1.3). The study also concluded that lower cervical disorders may play a role in the genesis of CeH.

PRF of the GON was evaluated by Gabrhelik et al. [30] and compared with the GON block (using a local anesthetic and steroid). A significant decrease in VAS scores and analgesic consumption were observed in both groups at 3 months, with long-term pain control (at 9 months) in the PRF group. Halim et al. [31] evaluated 86 patients with CeH who underwent lateral C1–C2 joint PRF. The percentage of patients with pain relief ≥ 50% at 2 months, 6 months, and 1 year was 50% (43/86), 50% (43/86), and 44.2% (38/86), respectively. Long-term pain relief at 6 months and 1 year was predicted by ≥ 50% pain relief at 2 months. The study concluded that PRF of the lateral C1–C2 joint was effective for pain relief in refractory CeH; however, outcome validation is limited by its retrospective nature and short follow-up period.

Hamer and Purath [32] evaluated 40 patients who received a bilateral RFA of the C2 DRG and were followed up for 6 months to one year. Pain relief was 100% in 35% of patients and ≥ 80% in 70% of patients. The mean duration of pain relief was 22.35 weeks. A total of 92.5% of patients reported satisfaction with the procedure and were willing to undergo the procedure again if the symptoms returned. The complication rate was 12–13%. Another study by Hamer and Purath [33] evaluated 23 patients with CeH who needed a repeat RFA of the C2 DRG and reported that the repeat RFA was effective. Compared to the first intervention, the repeat intervention showed either similar (in 59% of patients) or better (in 32% patients) effectiveness. Li and Feng [34] retrospectively evaluated 87 patients who underwent PRF of the C2 DRG and epidural steroid injection (ESI) and compared them with 52 patients who underwent only ESI. A significant reduction in the median pain score was observed in both groups at the 2-year follow-up. A significantly lowerVAS score, pain attack frequency, analgesic use, total pain score, and improved quality of life were observed in the PRF + ESI group than in the ESI group. Median pain relief lasted 8 months in the PRF + ESI group and 4 months in the ESI group, suggesting that the combination of PRF of the C2 DRG and ESI may be an effective and safe option for CeH. Lee et al. [35] evaluated 45 patients who underwent C2 DRG PRF after CeH recurrence 24 h after receiving a diagnostic C2 DRG block. A ≥ 50% reduction in pain was observed in 40% of patients (success group). Significantly more patients in the success group than in the failure group showed a positive diagnostic block. The study concluded that C2 DRG PRF is an effective treatment, especially for patients with definite pain reduction after the diagnostic C2 DRG block.

Among the upper three cervical spinal nerves, the C2 spinal nerve is more susceptible to injury [38]. The ventral rami of C2 innervates the AA joint, and also gives rise to LON. The GON arises from the medial aspect of the dorsal rami of the C2 spinal nerve. The C2 DRG, therefore, may be an effective target for PRF; however, evidence is limited due to the lack of randomized trials.

Cryoneurolysis

To achieve a long-lasting analgesic effect, freezing destruction of nerve conduction has been attempted for refractory cases of CeH. Kvarstein et al. [36] evaluated the clinical efficacy of occipital cryoneurolysis and compared it with local anesthetic and steroid injections. Despite a significant reduction in pain scores, pain intensity gradually increased after 6–7 weeks but had not returned to baseline by 18 weeks in both groups. No or minimal improvement was seen in health-related quality of life and psychological distress in both groups. After 18 weeks, majority of patients (74%) reported much or moderately improved global status, 55% of patients reported much or moderately improved headache intensity and 29% reported improved neck movement in cryoneurolysis group. These results indicate that the role of occipital cryoneurolysis in treating CeH may be questionable; however, further studies with larger sample sizes are required.

In this review, various interventions targeting different pain generators for the management of CeH have been described. Occipital nerve blocks (GON, LON) showed only limited evidence, as most of the studies were non-controlled and yielded only transient benefits. Facet joint intraarticular injections, anesthetic blocks of the upper cervical spinal nerves, AA joint injections, deep cervical plexus blocks, and cervical epidural blocks may be

https://doi.org/10.4097/kja.21328
effective treatments, they have generally only been shown to provide short-term relief, with limited or no long-term benefits. Further studies are needed to consolidate the role of freezing destruction of pain-generating fibers using cryoneurolysis. Radiofrequency lesioning may be preferable over other interventions because of its long duration of effect, better efficacy, and fewer side effects. Conventional RFA is neurodestructive and is associated with high complication rates, such as neuritis or deafferentation pain, which is not seen with PRF [32,33]. PRF, therefore, could be considered the preferred interventional approach for CeH management, given its better safety profile.

This systematic review had several limitations. First, most of the included studies were not RCTs. Second, the structure, inclusion/exclusion criteria, and outcomes assessed among the included studies were heterogeneous. Third, most of the included studies had a small sample size and short follow-up period. Additionally, there were flaws and inconsistencies in the design of both randomized and nonrandomized trials. Although a few studies showed promising outcomes of a particular intervention for the management of CeH, carefully designed, high-quality, large, prospective, randomized trials are needed to investigate the long-term benefits of various interventions for effectively managing CeH.

In conclusion, based on the available literature, occipital nerve (GON, LON) blocks, cervical facet intraarticular injections, AA joint injections, deep cervical plexus blocks, and cervical epidural steroid injections may be reasonable options for CeH treatment. Radiofrequency lesioning was found to be better with long-term positive outcomes, and pulsed therapy had better safety. However, our review revealed only limited evidence, and more RCTs are needed to provide more concrete evidence and to establish the relative efficacy of the various available interventions discussed for the management of CeH.

**Funding**

None.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Author Contributions**

Sonal Goyal (Conceptualization; Formal analysis; Methodology; Resources; Writing – original draft; Writing – review & editing)

Ajit Kumar (Conceptualization; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing)

Priyanka Mishra (Methodology; Resources; Supervision; Writing – review & editing)

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11. Grandhi RK, Kaye AD, Abd-Elsayed A. Systematic review of ra-
Using diagnostic testing to determine the presence or absence of a disease is essential in clinical practice. In many cases, test results are obtained as continuous values and require a process of conversion and interpretation and into a dichotomous form to determine the presence of a disease. The primary method used for this process is the receiver operating characteristic (ROC) curve. The ROC curve is used to assess the overall diagnostic performance of a test and to compare the performance of two or more diagnostic tests. It is also used to select an optimal cut-off value for determining the presence or absence of a disease. Although clinicians who do not have expertise in statistics do not need to understand both the complex mathematical equation and the analytic process of ROC curves, understanding the core concepts of the ROC curve analysis is a prerequisite for the proper use and interpretation of the ROC curve. This review describes the basic concepts for the correct use and interpretation of the ROC curve, including parametric/nonparametric ROC curves, the meaning of the area under the ROC curve (AUC), the partial AUC, methods for selecting the best cut-off value, and the statistical software to use for ROC curve analyses.

Keywords: Area under curve; Mathematics; Reference values; Research design; ROC curve; Routine diagnostic tests; Statistics.

Introduction

Using diagnostic testing to determine the presence or absence of a disease is an essential process in the medical field. To determine whether a patient is diseased or not, it is necessary to select the diagnostic method with the best performance be used by comparing various diagnostic tests. In many cases, test results are obtained as continuous values, which require conversion and interpretation into dichotomous groups to determine the presence or absence of a disease. At this time, determining the cut-off value (also called the reference value) to discriminate between normal and abnormal conditions is critical. The method that is mainly used for this process is the receiver operating characteristic (ROC) curve. The ROC curve aims to classify a patient’s disease state as either positive or negative based on test results and to find the optimal cut-off value with the best diagnostic performance. The ROC curve is also used to evaluate the overall diagnostic performance of a test and to compare the performance of two or more tests.

Although non-statisticians do not need to understand all the complex mathematical equations and the analytical process associated with ROC curves, understanding the core concepts of the ROC curve analysis is a prerequisite for the correct interpretation and application of analysis results. This review describes the basic concepts for the correct use and interpretation of the ROC curve, including how to draw an ROC curve, the difference between parametric and nonparametric ROC curves, the meaning of the area under
the ROC curve (AUC) and the partial AUC, the methods for selecting the best cut-off value, and the statistical software for ROC curve analysis.

**Sensitivity, specificity, false positive, and false negative**

To understand the ROC curve, it is first necessary to understand the meaning of sensitivity and specificity, which are used to evaluate the performance of a diagnostic test. Sensitivity is defined as the proportion of people who actually have a target disease that are tested positive, and specificity is the proportion of people who do not have a target disease that are tested negative. FP refers to the proportion of people that do not have a disease but are incorrectly tested positive, while FN refers to the proportion of people that have the disease but are incorrectly tested negative (Table 1). The ideal test would have a sensitivity and specificity equal to 1.0; however, this situation is rare in clinical practice since sensitivity and specificity tend to decrease when either of them increases.

As shown in Fig. 1, when a diagnostic test is performed, the group with the disease and the group without the disease cannot be completely divided, and overlapping exist. Fig. 1A shows two hypothetical distributions corresponding to a situation where the mean value of a test result is 75 in the diseased group and 45 in the non-diseased group. In this situation, if the cut-off value is set to 60, people with the disease who have a test result < 60 will be incorrectly classified as not having the disease (false negative). When a physician lowers the cut-off value to 55 to increase the sensitivity of the test, the number of people who will test positive increases (increased sensitivity), but the number of false positives also increases (Fig. 1B).

**What is the ROC curve?**

The ROC curve is an analytical method, represented as a graph, that is used to evaluate the performance of a binary diagnostic classification method. The diagnostic test results need to be classified into one of the clearly defined dichotomous categories, such as the presence or absence of a disease. However, since many test results are presented as continuous or ordinal variables, a reference value (cut-off value) for diagnosis must be set. Whether a disease is present can thus be determined based on the cut-off value. An ROC curve is used for this process.

The ROC curve was initially developed to determine between a signal (true positive result) and noise (false positive result) when analyzing signals on a radar screen during World War II. This method, which has been used for signal detection/discrimination, was later introduced to psychology [1,2] and has since been widely used in the field of medicine to evaluate the performance of diagnostic methods [3–6]. It has recently also been applied in various other fields, such as bioinformatics and machine learning [7,8].

The ROC curve connects the coordinate points using “1 – specificity (false positive rate)” as the x-axis and “sensitivity” as the y-axis for all cut-off values measured from the test results. The stricter the criteria for determining a positive result, the more points on the curve shift downward and to the left (Fig. 2, Point A). In contrast, if a loose criterion is applied, the point on the

---

**Table 1. The Decision Matrix**

<table>
<thead>
<tr>
<th>Predicted condition</th>
<th>Test (+)</th>
<th>Test (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease (+)</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Disease (−)</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

The receiver operating characteristic curve is drawn with the x-axis as 1 - specificity (false positive) and the y-axis as sensitivity; sensitivity = a / (a + b), specificity = d / (c + d), false negative = b / (a + b), false positive = c / (c + d), and accuracy = (a + d) / (a + b + c + d).

---

**Fig. 1.** Graphical illustrations of two hypothetical distributions for patients with or without disease of interest. The vertical line indicates the cut-point criterion to determine the presence of the disease. TN: true negative, TP: true positive, FN: false negative, FP: false positive.
The ROC curve has various advantages and disadvantages. First, the ROC curve provides a comprehensive visualization for discriminating between normal and abnormal over the entire range of test results. Second, because the ROC curve shows all the sensitivity and specificity at each cut-off value obtained from the test results in the graph, the data do not need to be grouped like a histogram to draw the curve. Third, since the ROC curve is a function of sensitivity and specificity, it is not affected by prevalence, meaning that samples can be taken regardless of the prevalence of a disease in the population [9]. However, the ROC curve also has some disadvantages. The cut-off value for distinguishing normal from abnormal is not directly displayed on the ROC curve and neither is the number of samples. In addition, while the ROC curve appears more jagged with a smaller sample size, a larger sample does not necessarily result in a smoother curve.

Types of ROC curves

The types of ROC curves can be primarily divided into non-parametric (or empirical) and parametric. Examples of the two curves are shown in Fig. 3, and the advantages and disadvantages of these two methods are summarized in Table 2. The parametric method is also referred to as the binary method. By expanding the sample size and connecting countless points, the parametric ROC curve forms the shape of a smooth curve [10]. This method estimates the curve using a maximum likelihood estimation when the two independent groups with different means and standard deviations follow a normal distribution or meet the normality assumption through algebraic conversion or square root transformation [11,12]. If the two normal distributions obtained from the two groups have considerable overlap, the ROC curve will be close to the 45° diagonal, whereas if only small portions of the two normal distributions overlap, the ROC curve will be located much farther from the 45° diagonal.

However, when the ROC curve is obtained using the parametric method, an improper ROC curve is obtained if the data does not meet the normality assumption or within-group variations are not similar (heteroscedasticity). An example of an improper parametric ROC curve is shown in Fig. 4. To use a parametric ROC curve, researchers must therefore check whether the outcome values in the diseased and non-diseased groups follow a normal dis-

![Fig. 2](https://doi.org/10.4097/kja.21209)  
**Fig. 2.** A receiver operating characteristic (ROC) curve connects coordinate points with 1 - specificity (= false positive rate) as the x-axis and sensitivity as the y-axis at all cut-off values measured from the test results. When a strict cut-off point (reference) value is applied, the point on the curve moves downward and to the left (Point A). When a loose cut-off point value is applied, the point moves upward and to the right (Point B). The 45° diagonal line serves as the reference line, since it is the ROC curve of random classification.

![Fig. 3](https://doi.org/10.4097/kja.21209)  
**Fig. 3.** The features of the empirical (nonparametric) and binormal (parametric) receiver operating characteristic (ROC) curves. In contrast to the empirical ROC curve, the binormal ROC curve assumes the normal distribution of the data, resulting in a smooth curve. For estimating the binormal ROC curve, the sample mean and sample standard deviation are calculated from the disease-positive group and the disease-negative group. The 45° diagonal line serves as the reference line, since it is the ROC curve of random classification.
distribution or a transformation is required to follow a normal distribution.

To overcome this limitation, a nonparametric ROC curve can be used since this method does not take into account the distribution of the data. This is the most commonly used ROC curve analysis method (also called the empirical method). For this method, the test results do not require an assumption of normality. The sensitivity and false positive rates calculated from the $2 \times 2$ table based on each cut-off value are simply plotted on the graph, resulting in a jagged line rather than a smooth curve.

Additionally, a semiparametric ROC curve is sometimes used to overcome the drawbacks of the nonparametric and parametric methods. This method has the advantage of presenting a smooth curve without requiring assumptions about the distribution of the diagnostic test results. However, many statistical packages do not include this method, and it is not widely used in the medical research.

### How is a ROC curve drawn?

Consider an example in which a cancer marker is measured for a total of 10 patients to determine the presence of cancer, and an empirical ROC curve is drawn (Table 3). If the measured value of the cancer marker is the same as or greater than the cut-off value (reference value), the patient is determined to have cancer, whereas if the measured value is less than the reference value, normal, and a $2 \times 2$ table is thus created. The sensitivity and specificity change depending on the applied reference value. If the reference value is increased, the specificity increases while the sensitivity decreases. For example, if the reference value for determining cancer is $\geq 43.3$, the sensitivity and specificity are calculated as 0.67 and 1.0, respectively (Table 3). To increase the sensitivity, the reference value for a cancer diagnosis is lowered. If the reference value is $\geq 29.0$, the sensitivity and specificity are 1.0 and 0.43, respectively. In this way, as the reference value is gradually increased or decreased, the proportion of positive cancer results varies, and each sensitivity and specificity pair can be calculated for each cut-off value. From these calculated pairs of sensitivity and specificity, a graph with “1 – specificity” as the x coordinate and “sensitivity” as the y coordinate can be created (Fig. 5). Some researchers draw an ROC curve by expressing the x-axis as “specificity” rather than “1 – specificity”. In this case, the values on the x-axis do not increase from 0 to 1.0, but decrease from 1.0 to 0.

### Table 2. Pros and Cons of the Nonparametric (Empirical) and Parametric Receiver Operating Characteristic Curve Approaches

<table>
<thead>
<tr>
<th></th>
<th>Nonparametric ROC curve</th>
<th>Parametric ROC curve</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td>No need for assumptions about the distribution of data. Provides unbiased estimates of sensitivity and specificity. The plot passes through all points. Uses all data. Computation is simple.</td>
<td>Shows a smooth curve. Compares plots at any sensitivity and specificity value.</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td>Has a jagged or staircase appearance. Compares plots only at observed values of sensitivity or specificity.</td>
<td>Actual data are discarded. Curve does not necessarily go through actual points. ROC curves and the AUC are possibly biased. Computation is complex.</td>
</tr>
</tbody>
</table>

ROC: receiver operating characteristic curve, AUC: area under the curve.
Table 3. An Example of Simple Data with Ten Patients for Drawing Receiver Operating Characteristic Curves

<table>
<thead>
<tr>
<th>Patient</th>
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<tr>
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</tr>
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Tumor marker (binary results)

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<th>(−)</th>
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<tr>
<td>Specificity</td>
<td>0.00</td>
<td>0.14</td>
<td>0.29</td>
<td>0.43</td>
<td>0.43</td>
<td>0.57</td>
<td>0.71</td>
<td>0.86</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Suppose three patients had biopsy-confirmed cancer diagnoses. The grey-colored values refer to the cases determined to be cancer according to each cut-off value highlighted in bold. The continuous test results can be transformed into binary categories by comparing each value with the cut-off (reference) value. As the cut-off value increases, the sensitivity for cancer diagnosis decreases and the specificity increases. At each cut-off value, one pair of sensitivity and specificity values can be obtained from the 2 × 2 table.

Fig. 5. Empirical (A) and parametric (B) receiver operating characteristic (ROC) curves drawn from the data in Table 3. Eleven labeled points on the empirical ROC curve correspond to each cut-off value to estimate sensitivity and specificity. A gradual increase or decrease of the cut-off values will change the proportion of disease-positive patients. Depending on the cut-off values, each sensitivity and specificity pair can be obtained. Using these calculated sensitivity and specificity pairs, a ROC curve can be obtained with “1 – specificity” as the x coordinates and “sensitivity” as the y coordinates.

The area under the curve (AUC)

The AUC is widely used to measure the accuracy of diagnostic tests. The closer the ROC curve is to the upper left corner of the graph, the higher the accuracy of the test because in the upper left corner, the sensitivity = 1 and the false positive rate = 0 (specificity = 1). The ideal ROC curve thus has an AUC = 1.0. However, when the coordinates of the x-axis (1 – specificity) and the y-axis...
correspond to 1 : 1 (i.e., true positive rate = false positive rate), a graph is drawn on the 45º diagonal (y = x) of the ROC curve (AUC = 0.5). Such a situation corresponds to determining the presence or absence of disease by an accidental method, such as a coin toss, and has no meaning as a diagnostic tool. Therefore, for any diagnostic technique to be meaningful, the AUC must be greater than 0.5, and in general, it must be greater than 0.8 to be considered acceptable (Table 4) [13]. In addition, when comparing the performance of two or more diagnostic tests, the ROC curve with the largest AUC is considered to have a better diagnostic performance.

The AUC is often presented with a 95% CI because the data obtained from the sample are not fixed values but rather influenced by statistical errors. The 95% CI provides a range of possible values around the actual value. Therefore, for any test to be statistically significant, the lower 95% CI value of the AUC must be > 0.5.

The CI of the AUC can be estimated using the parametric or nonparametric method. The binormal method proposed by Metz [14] and McClish and Powell [15] is used to estimate the CI of the AUC using the parametric approach. These methods use the maximum likelihood under the assumption of a normal distribution. Several nonparametric approaches have also been proposed to estimate the AUC of the empirical ROC curve and its variance. One such approach, the rank-sum test using the Mann-Whitney method, approximates the variance based on the exponential distribution [16]. However, the disadvantage of the rank-sum test is that it underestimates the variance when the AUC is close to 0.5 and overestimates the variance as the AUC approaches 1. To overcome this drawback, DeLong et al. [17] proposed a method of minimizing errors in variance estimates using generalized U-statistics without considering the normality assumptions used in the binormal method, which is provided in many statistical software packages.

Nonparametric AUC estimates for empirical ROC curves tend to underestimate the AUC on a discrete rating scale, such as a 5-point scale. Except when the sample size is extremely small, the parametric method is preferred even for discrete data, because the bias in the parametric estimates of the AUC is small enough to be negligible. However, if the collected data are not normally distributed, a nonparametric method is the correct option. For continuous data, the parametric and nonparametric estimates of the AUC have very similar values [18]. In general, when the sample size is large, the AUC estimate follows a normal distribution. Therefore, when determining whether there is a statistically significant difference between the two AUCs (AUC₁ vs. AUC₂), the test can be tested using the following Z-statistics. To determine whether an AUC (Aₑ) is significant under the null hypothesis, Z can be calculated by substituting Aₑ = 0.5.

\[
Z = (A₁ - Aₑ) / \sqrt{\text{Var}(AUC)}
\]

**Partial AUC (pAUC)**

When comparing the AUC of two diagnostic tests, if the AUC values are the same, this only means that the overall diagnostic performance of the two tests are the same and not necessarily that the ROC curves of the two tests are the same [19]. For example, suppose two ROC curves intersect. In this case, even if the AUCs of the two ROC curves are the same, the diagnostic performance of test A may be superior in a specific region of the curve, and test B may be superior in another region. In this case, the pAUC can be used to evaluate the diagnostic performance in a specific region (Fig. 6) [11,12].

As its name suggests, the pAUC is the area below some of the ROC curve. It is the region between two points of false positive rate (FPR), defined as the pAUC between the two FPRs (FPR₁ = e₁ and FPR₂ = e₂), which can be expressed as A (e₁ ≤ FPR ≤ e₂). For the entire ROC curve to be designated, e₁ = 0, e₂ = 1, and e₂ = e₁ = e is the sensitivity at the point where FPR = e. However, a potential problem with the pAUC is that the minimum possible value of the pAUC depends on the region along the ROC curve that is selected.

The minimum possible value of the pAUC can be expressed as \(\frac{1}{2} (e₂ - e₁) (e₂ + e₁)\) [15]. However, one issue is that the minimum pAUC value in the range 0 ≤ FPR ≤ 0.2 is \(\frac{1}{2} (0.2 - 0) (0.2 + 0) = 0.02\), whereas in the range 0.8 ≤ FPR ≤ 1.0, the minimum value of the pAUC is \(\frac{1}{2} (1.0 - 0.8)(1.0 + 0.8) = 0.18\). Therefore, unlike the AUC, in which the maximum possible value is always 1, the pAUC value depends on the two chosen FPRs. Therefore, the pAUC must be standardized. To do this, the pAUC is divided by the maximum value that the pAUC can have, which is called the partial area index [20]. The partial area index can be interpreted.

**Table 4. Interpretation of the Area Under the Curve**

<table>
<thead>
<tr>
<th>Area under the curve (AUC)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9 ≤ AUC</td>
<td>Excellent</td>
</tr>
<tr>
<td>0.8 ≤ AUC &lt; 0.9</td>
<td>Good</td>
</tr>
<tr>
<td>0.7 ≤ AUC &lt; 0.8</td>
<td>Fair</td>
</tr>
<tr>
<td>0.6 ≤ AUC &lt; 0.7</td>
<td>Poor</td>
</tr>
<tr>
<td>0.5 ≤ AUC &lt; 0.6</td>
<td>Fail</td>
</tr>
</tbody>
</table>

For a diagnostic test to be meaningful, the AUC must be greater than 0.5. Generally, an AUC ≥ 0.8 is considered acceptable.
Although the AUC is the same, the features of the ROC curves are not identical. Test B shows better performance in the high false-positive rate range than test A, whereas test A is better in the low false-positive range. In this example, the partial AUC (pAUC) can compare these two ROC curves at a specific false positive rate range.

as the average sensitivity in the selected FPR interval. In addition, the maximum pAUC between FPR$_1 = e_1$ and FPR$_2 = e_2$ is equal to $e_2 - e_1$, which is the width of the region when sensitivity = 1.0. By using the pAUC, it is possible to focus on the region of the ROC curve appropriate to a specific clinical situation. Therefore, the performance of the diagnostic test can be evaluated in a specific FPR interval that is appropriate to the purpose of the study.

**The sample size for the ROC curve analysis**

To calculate the sample size for the ROC curve analysis, the expected AUCs to be compared (namely, AUC$_1$ and AUC$_2$, where AUC$_2 = 0.5$ for the null hypothesis), the significance level ($\alpha$), power (1 − $\beta$), and the ratio of negative/positive results should be considered [16]. For example, if there are twice as many negative results as positive results, the ratio = 2, and if there is the same number of negative and positive results, the ratio = 1. If two tests are performed on the same group to evaluate test performance, the two ROC curves are not independent of each other. Therefore, two correlation coefficients are additionally needed between the two diagnostic methods both for cases showing negative results and those showing positive results [21]. The correlation coefficient required here is Pearson's correlation coefficient when the test result is measured as a continuous variable and Kendalls' tau (\(\tau\)) when measured as an ordinal variable [21].

**Determining the optimal cut-off value**

In general, it is crucial to set a cut-off value with an appropriate sensitivity and specificity because applying less stringent criteria to increase sensitivity results in a trade-off in which specificity decreases. Finding the optimal cut-off value is not simply done by maximizing sensitivity and specificity, but by finding an appropriate compromise between them based on various criteria. Sensitivity is more important than specificity when a disease is highly contagious or associated with serious complications, such as COVID-19. In contrast, specificity is more important than sensitivity when a test to confirm the diagnosis is expensive or highly risky. If there is no preference between sensitivity and specificity, or if both are equally important, then the most reasonable approach is to maximize them both. Since the methods introduced here are based on various assumptions, the choice of which method to use should be judged based on the importance of the sensitivity versus the specificity of the test. There are more than 30 methods known to find the optimal cut-off value [22]. Some of the commonly used methods are introduced below.

**Youden's J statistic**

Youden’s J statistic refers to the distance between the 45° diagonal and the ROC curve while moving the 45° diagonal (a straight line with a slope of 1) in the coordinate (0, 1) direction (Fig. 7A). Youden’s J statistic can be calculated as follows, where the point at which this value is maximized is determined as the optimal cut-off value [23].

\[
J = Se + Sp - 1
\]

**Euclidean distance**

Another method for determining the optimal reference value is to use the Euclidean distance from the coordinate (0, 1), which is also called the upper-left (UL) index [24]. For this method, the optimal cut-off value is determined using the basic principle that the AUC value should be large. Therefore, the distance between the coordinates (0, 1) and the ROC curve should be minimized [25,26]. The Euclidean distance is calculated as follows:

\[
\text{Euclidean distance} = \sqrt{(1 - Se)^2 + (1 - Sp)^2}
\]
Fig. 7. Figures illustrating the various methods to select the best cut-off values. (A) Youden J statistics, (B) Euclidean distance to the upper-left corner, and (C) maximum multiplication of sensitivity and specificity.

The point at which this value is minimized is considered the optimal cut-off value. The Euclidean distance on the ROC curve is shown in Fig. 7B.

Accuracy

Accuracy refers to the proportion of the cases that are accurately classified, as shown in Table 1.

\[
\text{Accuracy} = \frac{\text{True positive number} + \text{True negative number}}{\text{Total number}}
\]

This definition assumes that all correctly classified results (whether it is true positive or true negative) are of equal value, and all misclassified results are equally undesirable. However, this is often not the case. The costs of false-positive and false-negative classifications are rarely equivalent; the more significant the cost difference between false positive and false negative results, the more likely that the accuracy distorts the clinical usefulness of the test results. Accuracy is highly dependent on the prevalence of a disease in the sample; therefore, even when the sensitivity and specificity are low, the accuracy may be high [27]. In addition, this method has a disadvantage because, as sensitivity and specificity change, there may be two or more points at which this value is maximized.

Index of union (IU)

IU uses the absolute difference between the diagnostic measurement and the AUC value to minimize the misclassification rate, calculated using the following formula [28]:

\[
IU = (|S_{-}\text{AUC}| + |S_{-}\text{AUC}|)
\]

IU is a method for finding the point at which the sensitivity and specificity are simultaneously maximized. It is similar to the Euclidean distance; however, it differs in that it uses the absolute differences between the AUC value and diagnostic accuracy measurements (sensitivity and specificity). This method does not require complicated calculations since it only involves checking whether the sensitivity and specificity at the optimal cut-off value are sufficiently close to the AUC values. In addition, the IU has been found to have a better diagnostic performance compared to the other methods in most cases [28].

Cost approach

The cost approach is a method for finding the optimal cut-off value that takes into account the benefits of correct classification or the costs of misclassification. This method can be used when the costs of true positives (TPs), true negatives (TNs), false positives (FPs), and false negatives (FNs) of a diagnostic test are known. The costs here can be medical or financial and can be considered from a patient and/or social perspective. When determining the cut-off value using the cost approach, there are two ways; to calculate the cost itself [27], or use the cost index \( f_m \) [29]. These are calculated as follows:

\[
\text{Cost} = C_{\text{TN}}(1 - S_{\text{e}}) \Pr + C_{\text{FP}}(1 - S_{\text{e}})(1 - \Pr) + C_{\text{TP}}S_{\text{e}} \Pr + C_{\text{FN}}S_{\text{p}}(1 - \Pr)
\]

\[
f_m = S_{\text{e}} - \left( \frac{1 - \Pr}{\Pr} \times \frac{C_{\text{FP}} - C_{\text{TN}}}{C_{\text{TP}} - C_{\text{TN}}} \right) (1 - S_{\text{e}})
\]
where Pr is prevalence and \( C_{FP}, C_{TN}, C_{FN}, \) and \( C_{TP} \) refer to the costs of FPs, TNs, FNs, and TPs, respectively. These four costs should be expressed as a common unit. When the cost index \( f_m \) is maximized, the average cost is minimized, and this point is considered the optimal cut-off value.

Another method for determining the optimal cut-off value in terms of cost is to use the misclassification cost term (MCT). Considering only the prevalence of the disease, the \( C_{FP} \) and the \( C_{FN} \), the point at which the MCT is minimized is determined as the optimal cut-off value \([29]\) and expressed as follows:

\[
\text{MCT} = \frac{C_{FN}}{C_{FP}} \times \text{Pr} (1 - \text{Se}) + (1 - \text{Pr})(1 - \text{Sp})
\]

Positive likelihood ratio (LR\(^{+}\)) and negative likelihood ratio (LR\(^{-}\))

LR\(^{+}\) is the ratio of true positives to false positives, and LR\(^{-}\) is the ratio of false negatives to true negatives.

\[
\text{LR}^{+} = \frac{\text{TP}}{\text{FP}} = \frac{\text{Se}}{(1 - \text{Sp})} \quad \text{LR}^{-} = \frac{\text{FN}}{\text{TN}} \frac{(1 - \text{Se})}{\text{Sp}}
\]

Researchers can choose a cut-off value that either maximizes LR\(^{+}\) or minimizes LR\(^{-}\).

Maximum product of sensitivity and specificity

For this method, the point at which the product of Se and Sp is maximized is considered the optimal cut-off value.

\[
\text{Maximum product} = \max [\text{Se} \times \text{Sp}]
\]

This can also be represented graphically, as shown in Fig. 7C. A square can be obtained whose vertex is on the line connecting the unit square’s upper left and lower right corners within the ROC curve (Se = Sp line). When this square meets the ROC curve, Se × Sp is maximized.

Maximum sum of sensitivity and specificity

For this method, the point at which the sum of Se and Sp is maximized is considered the optimal cut-off value.

\[
\text{Maximum sum} = \max [\text{Se} + \text{Sp}]
\]

At the point where the summation value is maximized, Youden’s index \((\text{Se} + \text{Sp} - 1)\) and the difference between the true positives (Se) and false positives \((1 - \text{Sp})\) are also maximized \([25]\).

This method is straightforward; however, the drawback is that as the Se and Sp change, there may be more than one point at which this value is maximized. When there are two or more points at which the summed value is maximized, the researcher must decide whether to determine the optimal cut-off value based on the sensitivity or the specificity.

Number needed to misdiagnose (NNM)

This method refers to the number of patients required to obtain one misdiagnosis when conducting a diagnostic test. In other words, if NNM = 10, it means that ten people must be tested to find one misdiagnosed patient. The higher the NNM, the better the test performance. NNM is calculated as follows, and the point at which the NNM is maximized can be selected as the optimal cut-off value \([30]\):

\[
\text{NNM} = \frac{1}{\text{FN} + \text{FP}} = \frac{1}{\text{Pr} (1 - \text{Se}) + (1 - \text{Pr})(1 - \text{Sp})}
\]

Statistical program for the ROC curve analysis

Statistical programs used to perform the ROC curve analysis include various commercial software programs such as IBM SPSS, MedCalc, Stata, and NCSS and open-source software such as R. Most statistical analysis software programs provide basic ROC analysis functions. However, the functions provided by each software product are slightly different. IBM SPSS, the most widely used commercial software, can provide fundamental statistical analyses for ROC curves, such as plotting ROC curves, calculating the AUC, and CIs with statistical significance. However, IBM SPSS does not include various functions for optimal cut-off values and does not provide a sample size calculation. Stata provides a variety of functions for ROC curve analyses, including the pAUC, multiple ROC curve comparisons, optimal cut-off value determination using Youden’s index, and multiple performance measures. MedCalc, as the name suggests, is a software developed specifically for medical research. MedCalc provides a sample size estimation for a single diagnostic test and includes various analytical techniques to determine the optimal cut-off value but does not provide a function to calculate the pAUC.

Unlike commercial software packages, the R program is a free, open-source software that includes all the functions for ROC curve analyses using packages such as ROCR \([31]\), pROC \([32]\), and OptimalCutpoints \([22]\). Among the R packages, the ROCR is one of the most comprehensive packages for analyzing ROC curves and includes functions to calculate the AUC with CIs;
however, options for selecting the optimal cut-off value are very limited. The pROC provides more comprehensive and flexible functions than the ROC. The pROC can be used to compare the AUC with the pAUC using various methods and it provides CIs for sensitivity, specificity, the AUC, and the pAUC. Similar to the ROCR, the pROC also provides some functions for determining the optimal cut-off value, which can be determined using Youden’s index and the UL index. The pROC can also be used to calculate the sample size required for a single diagnostic test or to compare two diagnostic tests. OptimalCutpoints is a sophisticated R package specially developed to determine the optimal cut-off value. It has the advantage of providing 34 methods for determining the optimal cut-off value.

Although these R packages have a considerable number of functions, they require good programming knowledge of the R language. Therefore, for someone who is not an R user, working with a command-based interface may be challenging and time-consuming. Therefore, a web-based tool that combines several R packages has recently been developed to overcome these shortcomings, enabling a more straightforward ROC analysis. The web tool for the ROC curve analysis based on R, which includes easyROC and plotROC [33,34], is a web-based application that uses the R packages plyr, pROC, and OptimalCutpoints to perform ROC curve analyses, extending the functions of multiple ROC packages in R so that researchers can perform ROC curve analyses through an easy-to-use interface without writing R code. The functions of various statistical packages for ROC curve analyses are compared and presented in Table 5.

### Summary

The ROC curve is used to represent the overall performance of a diagnostic test by connecting the coordinate points with “1 – specificity” (= false positive rate) as the x-axis and “sensitivity” as the y-axis for all cut-off point at which the test results are measured. It is also used to determine the optimal cut-off value for diagnosing a disease. The AUC is a measure of the overall performance of a diagnostic test and can be interpreted as the average value of sensitivities for all possible specificities. The AUC has a value between 0 and 1 but is meaningful as a diagnostic test only when it is > 0.5. The larger the value, the better the overall performance of the test. Since nonparametric estimates of the AUC tend to be underestimated with discrete grade scale data, whereas parametric estimates of the AUC have a low risk of bias unless the sample size is very small, it is recommended to use parametric estimates for discrete grade scale data. When evaluating the diagnostic performance of a test only in some regions of the overall ROC curve, the pAUC should be used in specific FPR regions.

Youden’s index, Euclidean distance, accuracy, and cost index can be used to determine the optimal cut-off value. However, the approach should be selected according to the clinical situation that the researcher intends to analyze. Various commercial programs and R packages as well as a web tool based on R can be used for ROC curve analyses.

In conclusion, the ROC curve is a statistical method used to determine the diagnostic method and the best cut-off value showing the best diagnostic performance. The best diagnostic test method and the optimal cut-off value should be determined using the appropriate method.

### Table 5. Comparison of the Statistical Packages for Receiver Operating Characteristic Curve Analyses

<table>
<thead>
<tr>
<th>Statistical packages</th>
<th>ROC plot</th>
<th>Confidence interval</th>
<th>pAUC</th>
<th>Multiple comparisons</th>
<th>Cut-off values</th>
<th>Sample size</th>
<th>Open source</th>
<th>Web tool access</th>
<th>User interface</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Commercial program</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>IBM SPSS (ver. 25)</td>
<td>○</td>
<td>○</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>○</td>
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</tr>
<tr>
<td>STATA (ver. 14)</td>
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<td>MedCalc (ver. 19.4.1)</td>
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<td>×</td>
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<td><strong>Free program</strong></td>
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<td>OptimalCutpoints</td>
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<td>○</td>
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<td>○</td>
<td>○</td>
<td>×</td>
<td>○</td>
</tr>
<tr>
<td>pROC (ver. 1.17.0.1)</td>
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<td>○</td>
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<td>○</td>
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<td>○</td>
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<tr>
<td>easyROC (ver. 1.3.1)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>plotROC (ver. 2.2.1)</td>
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<td>×</td>
<td>○</td>
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<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

This table was adapted and modified from Goksuluk et al. [33]. ROC: receiver operating characteristic, pAUC: partial area under the ROC curve. ○: possible, ×: impossible.

https://doi.org/10.4097/kja.21209

Francis Sahgun Nahm · Receiver operating characteristic curve
Acknowledgements

The author would like to thank Ms. Mihee Park at the Seoul National University Bundang Hospital for her assistance in editing the figures included in this paper.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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https://doi.org/10.4097/kja.21209


Comparison of upper and lower body forced air blanket to prevent perioperative hypothermia in patients who underwent spinal surgery in prone position: a randomized controlled trial

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Background: We compared upper- and lower-body forced-air blankets in terms of their ability to prevent perioperative hypothermia, defined as a reduction in body temperature to < 36.0°C, during the perioperative period in patients undergoing spine surgery in the prone position.

Methods: In total, 120 patients scheduled for elective spine surgery under general anesthesia were divided into an upper-warming group (n = 60) and a lower-warming group (n = 60). After inducing anesthesia and preparing the patient for surgery, including prone positioning, the upper and lower bodies of the patients in the upper- and lower-warming groups, respectively, were warmed using a forced-air warmer with specified upper and lower blankets. Body temperature was measured using a tympanic membrane thermometer during the pre- and post-operative periods and using a nasopharyngeal temperature probe during the intraoperative period. Patients were evaluated in terms of shivering, thermal comfort, and satisfaction in the post-anesthesia care unit (PACU).

Results: The incidence of intraoperative and postoperative hypothermia was lower in the upper-warming group than in the lower-warming group ([55.2% vs. 75.9%, P = 0.019] and [21.4% vs. 49.1%, P = 0.002]). Perioperative body temperature was higher in the upper-warming group (P < 0.001). However, intraoperative blood loss, postoperative thermal comfort scale and shivering scores, patient satisfaction, and PACU duration were similar in the two groups.

Conclusions: The upper-body blanket was more effective than the lower-body blanket for preventing perioperative hypothermia in patients who underwent spine surgery in the prone position.

Keywords: Body temperature; Forced-air warming; Hypothermia; Lower body; Prone position; Spine surgery; Upper body.

Introduction

The rate of perioperative hypothermia, defined as a reduction in body temperature to < 36.0°C during the perioperative period, is typically 50–90%, even during short and simple surgeries [1,2]. Managing perioperative body temperature is very important be-
cause even mild hypothermia can cause complications, including cardiac morbidity, poor drug metabolism, delayed recovery from anesthesia, greater blood loss in association with platelet dysfunction and coagulopathy, delayed wound recovery, and greater frequency of surgical site infections [3]. A forced-air warmer is the most commonly used device to prevent perioperative hypothermia and provides warmth not only by transferring convective heat to the body but also by preventing heat loss from the covered area [4–6].

Patients undergoing spine surgery in the prone position tend to be susceptible to hypothermia because of the long surgical duration and large exposed skin surface area associated with the procedure [6]. Perioperative hypothermia is also associated with ophthalmic complications during spine surgery in the prone position, so preventing hypothermia is important [7]. The effectiveness of forced-air warming underbody blankets has been reported, but they are more expensive than conventional warming devices and thus not particularly popular [8]. Therefore, forced-air warming over-body blanket for the upper or lower body is often used, depending on the location of the surgical site.

Previous studies have reported that lower-body warming is more effective in the supine position because of the larger body surface area (BSA) covered [9,10]. However, another study reported that, in the lateral decubitus position, upper-body warming was more effective than lower-body warming due to the padding between the legs in the latter case [11]. According to a preliminary retrospective study conducted at our institution, upper-body warming results in a significantly lower incidence of hypothermia compared with lower-body warming, during spine surgery in the prone position (unpublished data). However, few studies have compared the effectiveness of upper- and lower-body warming during spine surgery in the prone position [12]. We hypothesized that an upper-body blanket would be superior to a lower-body blanket to prevent perioperative hypothermia in patients undergoing spine surgery in the prone position. Thus, we compared the warming effects of upper- and lower-body forced-air blankets in patients undergoing spine surgery in the prone position.

Materials and Methods

This prospective randomized controlled trial was approved by the institutional ethics committee (SCHUH 2018-12-009-001) of Soonchunhyang university hospital in Seoul and registered at the Clinical Research Information Service (CRIS) clinical trials registry (KCT0003728). The trial was performed from March 2019 to August 2019. All patients were given information about the trial, and all provided written informed consent. This manuscript adheres to the relevant CONSORT guidelines. The research was performed following the ethical principles for medical research involving human subjects of the 1964 Declaration of Helsinki and all of its subsequent revisions (revised 2013).

Study participants and inclusion/exclusion criteria

The trial included 120 patients (aged ≥ 19 years) with an American Society of Anesthesiologists physical status (ASA-PS) of I–III who were scheduled to undergo elective spine surgery in the prone position. Exclusion criteria were body mass index (BMI) > 35 kg/m², preoperative body temperature > 38°C or < 36°C, and pregnancy.

Randomization and masking

Using Excel software (2016; Microsoft Corp., USA), patients were randomly allocated to the upper- or lower-warming groups (both n = 60) by a computer-generated blocked randomization scheme (block size 4, 6; 1 : 1 allocation ratio). The anesthesiologists (who anesthetized the patients and supervised the warming) were not blinded to the group allocation, whereas the patients and study nurse (who collected the pre- and post-operative data) were blinded.

General procedures

After arrival in the operating room, all patients were fully covered with a cotton blanket. Standardized monitoring and anesthesia induction (using 1–2 mg/kg 1% propofol and 0.6 mg/kg rocuronium) were performed. Catheters were inserted into the urethra, radial artery, or internal jugular vein as needed, with minimal exposure of the skin to ambient air. Then, the patient was placed in the prone position. Standardized anesthesia was maintained using desflurane and remifentanil.

After prone positioning, the specified upper and lower blankets were placed over the back and both arms in the upper-warming group, and over the lower buttocks and both legs in the lower-warming group by the anesthesiologist. As most surgical fields for spine surgery are from the T4 dermatome to the coccyx, a Warm Touch™ upper-body blanket (Medtronic, Ireland) was taped above the T4 spinous process level, and covered the upper extremities and upper trunk above the T4 dermatome. A Warm Touch™ lower-body blanket (Medtronic) was taped below the coccyx and covered both legs and the lower buttocks below the coccyx. The entire body of all patients was covered with a surgical drape, except for the surgical field and head. After surgical drape-
ing, intraoperative warming using a forced-air warmer (Warm-Touch™ WT 6000 Warming Unit; Medtronic) was applied until the end of the surgery. The temperature was adjusted to 45°C when the core body temperature was < 36.5°C, and to 40°C when the core body temperature was 36.5–37.5°C. The warmer was turned off when the core body temperature was > 37.5°C. A breathing circuit that allows for intraoperative heating/humidification was used in all patients; no other warming devices were used.

At the end of surgery, we removed the forced-air blanket, placed the patient in the supine position, and warmed the whole body with a cotton blanket during emergence from anesthesia. The patient’s consciousness and spontaneous respiration were restored, and the nasopharyngeal thermometer and tracheal tube were removed. The patients were transferred to the post-anesthesia care unit (PACU). If tympanic temperature measurement and the postoperative evaluations indicated hypothermia, warming was actively performed using the forced-air warmer as described above.

Measurements

The baseline patient characteristics were recorded preoperatively, including age, sex, weight, height, BMI, ASA-PS, and level of spine surgery. BSA was calculated using the Dubois formula.

To evaluate the primary endpoint of the incidence of perioperative hypothermia, tympanic temperature was measured using a Thermoscan®, an infrared tympanic thermometer (IRT 4020; Braun, USA), by a masked nurse in the pre-anesthetic holding area, and in the PACU every 10 min (up to 30 min) after arrival in the PACU [13]. The right and left tympanic temperatures were measured, and the average value was calculated. The nasopharyngeal temperature was measured using a thermometer (ETP1040; Ewha Biomedics, Korea) at a depth of 9–10 cm in the nasopharynx immediately after induction of anesthesia [14]. Readings were obtained every 15 min till the end of surgery.

The secondary endpoints were perioperative temperature changes, postoperative thermal comfort (100-mm visual analogue scale: 0 mm = coldest imaginable, 50 mm = pleasant, 100 mm = warmest imaginable) and shivering (0 = no shivering; 1 = intermittent, low intensity; 2 = moderate shivering; 3 = continuous intense shivering) scores, patient satisfaction regarding temperature management (0 = very dissatisfied, 1 = dissatisfied, 2 = neutral, 3 = satisfied, 4 = very satisfied), and PACU duration. All patients were trained in the use of the thermal comfort scale in the ward on the day before surgery. A masked nurse asked the patient to complete the thermal comfort and shivering scales every 10 min following arrival in the PACU (up to 30 min). Before leaving the PACU, the patients were asked to rate the satisfactoriness of the perioperative temperature on a five-point Likert scale. The length of stay in the PACU and any adverse effects of forced-air warming were also recorded.

The ambient temperatures in the operating room and PACU were recorded on arrival and discharge, and the average temperature was calculated. The durations of the ‘unwarmed’ (from arrival in the operating room to the start of intraoperative warming) and anesthetic periods were recorded. The intraoperative fluid volume, blood loss, and transfusion requirement were also recorded by the anesthesiologist.

Sample size and statistical analyses

Min et al. [11] reported that the incidence of intraoperative hypothermia in the lateral decubitus position during thoracoscopic surgery was 33.87% in their upper-warming group and 57.38% in their lower-warming group. Assuming that the incidence of intraoperative hypothermia would be reduced by a similar degree in our study, we calculated that 60 patients per group were required with an α of 0.05 for a one-tailed test, power of 80%, and a dropout rate of 10%.

Statistical analyses were performed using SPSS for Windows software (version 26.0; IBM Corp., USA). The two groups were compared using Student’s t-test or the Mann–Whitney rank-sum test for continuous data, after checking for normality with the Shapiro–Wilk test, and by the chi-square or Fisher’s exact test for categorical data. All analyses in this trial were conducted in an intention-to-treat manner because dropout data were missing.

Perioperative body temperature data were plotted and analyzed using a mixed-effects model with a first-order autoregressive covariance structure. The fixed effects in the mixed-effects model included group, time, and the interaction between group and time. Subjects were included as a random effect. Post-hoc testing using Bonferroni’s method for pairwise group comparisons was performed when the results of the mixed-effects model were significant.

Multivariable logistic regression analysis was performed post-hoc to identify variables affecting intraoperative hypothermia (< 36.0°C) and severe intraoperative hypothermia (< 35.0°C). Variations in factors of BMI, BSA, weight, height, and the BSA/weight ratio were more than 10.0, which caused multicollinearity in the multiple regression. Therefore, the BSA/weight ratio was selected as the morphometric variable. In total, 11 variables were included (BSA/weight × 1,000, group, sex, age, ASA-PS, anesthetic duration, surgery type [ > 2 levels], unwarmed duration (from
arrival in the operating room to the start of intraoperative warming), operating room ambient temperature, preoperative body temperature, and fluid administration (> 1,000 ml) as independent variables in the multivariable logistic regression. The backward stepwise elimination method was used to select the variables based on the log-likelihood ratio.

Continuous data are presented as mean and standard deviation (SD) or median and 25th and 75th percentiles, and categorical data as frequencies with percentages. A P value < 0.05 was considered significant, and a temperature difference between the intervention and control groups of 0.2°C was defined as significant based on the National Institutes for Health and Clinical Excellence guidelines [15].

Results

In total, 126 patients were screened. Three patients were excluded because they met the exclusion criteria and another three refused to participate. Thus, 120 patients were ultimately enrolled in the study and were divided randomly into the upper- and lower-warming groups (both n = 60). Two patients in the upper-warming group dropped out just before surgery (one due to hyperthermia [38.4°C] and one due to canceled surgery). Continuous intraoperative warming was stopped in two patients in the lower-warming group (due to a machine error in one patient and failure to record intraoperative core temperature data due to a thermometer module error in another patient). Therefore, data from 116 patients were analyzed (58 patients in each group). Two patients in the upper-warming group and one in the lower-warming group were transferred to the intensive care unit for close postoperative observation by the surgeon; thus, postoperative data from these three patients could not be obtained. Moreover, thermal comfort and satisfaction-scale data could not be obtained in two patients (one each in the upper- and lower-warming groups) who showed postoperative delirium in the PACU (Fig. 1).

The baseline characteristics of the patients, and the level of spine surgery, duration of anesthesia, duration of the unwarmed period (from arrival in the operating room to the start of intraoperative warming), body temperature upon arrival in the pre-anesthetic holding area, ambient temperature of the operating room and PACU, and fluid volume are shown in Table 1. No clinically significant differences between the two groups in these characteristics were observed (Table 1).

The incidence of intraoperative hypothermia, was significantly lower in the upper-warming group than in the lower-warming group (55.2% vs. 75.9%, OR 0.392 [0.177, 0.866], P = 0.019). The

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**Table 1.** Baseline characteristics of the patients, and the level of spine surgery, duration of anesthesia, duration of the unwarmed period (from arrival in the operating room to the start of intraoperative warming), body temperature upon arrival in the pre-anesthetic holding area, ambient temperature of the operating room and PACU, and fluid volume.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Upper-warming Group</th>
<th>Lower-warming Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of spine surgery</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Duration of anesthesia</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Duration of unwarmed period</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Body temperature upon arrival</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ambient temperature of OR</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fluid volume</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

---

**Fig. 1.** CONSORT diagram. ICU: intensive care unit.
### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Upper-warming group (n = 58)</th>
<th>Lower-warming group (n = 58)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69 (59.8, 77.0)</td>
<td>69 (59.8, 76.3)</td>
<td>0.840</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>24/34</td>
<td>26/32</td>
<td>0.708</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.6 ± 11.7</td>
<td>65.1 ± 12.99</td>
<td>0.266</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.3 ± 8.0</td>
<td>160.1 ± 9.3</td>
<td>0.276</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 3.49</td>
<td>25.2 ± 3.12</td>
<td>0.592</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.631 ± 0.171</td>
<td>1.681 ± 0.203</td>
<td>0.152</td>
</tr>
<tr>
<td>ASA-PS classification (I/II/III)</td>
<td>11/33/14</td>
<td>16/33/9</td>
<td>0.366</td>
</tr>
<tr>
<td>Level of spine surgery</td>
<td></td>
<td></td>
<td>0.787</td>
</tr>
<tr>
<td>Discectomy</td>
<td>7 (12.1)</td>
<td>7 (12.1)</td>
<td></td>
</tr>
<tr>
<td>PD only</td>
<td>19 (32.8)</td>
<td>19 (32.8)</td>
<td></td>
</tr>
<tr>
<td>Single-level PLIF and PD</td>
<td>22 (37.9)</td>
<td>20 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Two-level PLIF and PD</td>
<td>4 (6.9)</td>
<td>8 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Multilevel lumbar surgery ( &gt; 2 levels)*</td>
<td>3 (5.2)</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Expanded to thoracic level ( &gt; 2 levels)*†</td>
<td>3 (5.2)</td>
<td>3 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>183 (130.0, 250.0)</td>
<td>200 (123.8, 289.8)</td>
<td>0.469</td>
</tr>
<tr>
<td>Duration of unwarmed period (min)‡</td>
<td>38 ± 10.5</td>
<td>38 ± 10.6</td>
<td>0.951</td>
</tr>
<tr>
<td>Initial body temperature (°C)</td>
<td>37.0 ± 0.37</td>
<td>36.9 ± 0.34</td>
<td>0.570</td>
</tr>
<tr>
<td>OR temperature (°C)</td>
<td>21.3 ± 0.94</td>
<td>21.3 ± 0.95</td>
<td>0.713</td>
</tr>
<tr>
<td>PACU temperature (°C)§</td>
<td>26.0 (24.85, 26.48)</td>
<td>25.8 (24.75, 26.50)</td>
<td>0.598</td>
</tr>
<tr>
<td>Fluid volume (ml)</td>
<td>600 (300, 1225)</td>
<td>750 (300, 1163)</td>
<td>0.474</td>
</tr>
</tbody>
</table>

Values are presented as numbers (%) for categorical data, mean ± SD or median (Q1, Q3) as appropriate for continuous data. *With or without instrumentation. †Some multilevel surgeries included the lower thoracic spine. ‡Unwarmed period is defined as the period from arrival in the operating room to the start of intraoperative warming, and corresponds to the period of exposure to the operating room ambient temperature without warming after arrival in the operating room. §The ambient temperature of the PACU was maintained at 26 ± 1°C according to institutional regulations. BMI: body mass index, BSA: body surface area, ASA-PS: American Society of Anesthesiologists physical status, OR: operating room, PACU: post-anesthesia care unit, PD: posterior decompression, PLIF: posterior lumbar inter-body fusion.

### Table 2. Intraoperative and Postoperative Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Upper-warming group</th>
<th>Lower-warming group</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative variables</td>
<td>(n = 58)</td>
<td>(n = 58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative hypothermia</td>
<td>32 (55.2)</td>
<td>44 (75.9)</td>
<td>0.392 (0.177, 0.866)</td>
<td>0.019</td>
</tr>
<tr>
<td>Severity of intraoperative hypothermia</td>
<td></td>
<td></td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Mild (35.5–36.0°C)</td>
<td>20 (34.5)</td>
<td>21 (36.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (35.0–35.4°C)</td>
<td>8 (13.8)</td>
<td>9 (15.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (34.5–34.9°C)</td>
<td>3 (5.2)</td>
<td>10 (17.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very severe (&lt; 34.5°C)</td>
<td>0 (0.0)</td>
<td>4 (6.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of intraoperative hypothermia (min)</td>
<td>20.0 (0, 112.5)</td>
<td>102.5 (11.3, 186.3)</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>150 (93, 320)</td>
<td>200 (100, 400)</td>
<td></td>
<td>0.241</td>
</tr>
<tr>
<td>Transfusion (n)</td>
<td>0</td>
<td>2 (3.4)</td>
<td></td>
<td>0.496</td>
</tr>
<tr>
<td>Objective PACU variables</td>
<td>(n = 56)</td>
<td>(n = 57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACU hypothermia</td>
<td>12 (21.4)</td>
<td>28 (49.1)</td>
<td>0.282 (0.124, 0.643)</td>
<td>0.002</td>
</tr>
<tr>
<td>Shivering score (0/1/2)</td>
<td>53/3/0</td>
<td>53/4/0</td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>LOS at PACU (min)</td>
<td>37 (34.3, 45.0)</td>
<td>40 (34.0, 47.5)</td>
<td></td>
<td>0.296</td>
</tr>
<tr>
<td>Subjective PACU variables</td>
<td>(n = 55)</td>
<td>(n = 56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest TCS</td>
<td>50 (50, 50)</td>
<td>50 (50, 50)</td>
<td></td>
<td>0.808</td>
</tr>
<tr>
<td>Lowest TCS</td>
<td>50 (50, 50)</td>
<td>50 (50, 50)</td>
<td></td>
<td>0.073</td>
</tr>
<tr>
<td>Patient satisfaction (4/3/2)</td>
<td>32/21/2</td>
<td>29/22/5</td>
<td></td>
<td>0.485</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) as appropriate for continuous data or numbers (%) for categorical data. Hypothermia was defined as a reduction in body temperature to < 36.0°C. TCS: thermal comfort scale, LOS: length of stay, PACU: post-anesthesia care unit.

[https://doi.org/10.4097/kja.21087](https://doi.org/10.4097/kja.21087)
severity of intraoperative hypothermia differed significantly between the two groups \( (P = 0.018) \) (Table 2). The incidence of immediate postoperative hypothermia in the PACU was lower in the upper-warming group than in the lower-warming group \( (21.4\% \text{ vs. } 49.1\%) \), OR \( 0.282 \) [0.124, 0.643], \( P = 0.002 \) (Table 2).

Intraoperative blood loss and the transfusion requirement did not differ between the two groups \( (P = 0.241 \text{ and } P = 0.496, \text{ respectively}) \). Postoperative shivering score \( (P = 1.000) \) and the highest and lowest thermal comfort scale scores \( (P = 0.808 \text{ and } P = 0.073, \text{ respectively}) \) in the PACU also did not differ significantly between the groups. Satisfaction with the warming protocol did not differ between the groups \( (P = 0.485) \), nor did the length of stay in the PACU \( (P = 0.296) \) (Table 2). No adverse effects from forced-air warming, such as skin irritation or burns, were observed in any patient.

The change in body temperature over time differed significantly between the two groups \( (P < 0.001) \). The group difference from 75 min after induction of anesthesia to the end of recovery was significant according to the Bonferroni post-hoc test at \( > 0.2°C \) (which has been defined as a significant clinical difference in hypothermic patients) \cite{15}. The significant decrease in body temperature compared with the preoperative temperature persisted throughout the recovery period. The greatest decrease in body temperature in the upper-warming group occurred 60 min after inducing anesthesia \( (0.98°C) \); it occurred after 135 min \( (1.23°C) \) in the lower-warming group (Fig. 2).

Hosmer and Lemeshow’s goodness-of-fit test showed that the regression models for intraoperative hypothermia \( (< 36.0°C) \) and severe intraoperative hypothermia \( (< 35.0°C) \) were suitable \( (P = 0.704, P = 0.956, \text{ respectively}) \), and the models were statistically significant \( (\text{both } P < 0.001) \). Six variables were independently related to intraoperative hypothermia. Upper-warming \( \text{(OR 0.221 [0.072, 0.683], } P = 0.009) \), high ambient temperature \( \text{(OR 0.280 [0.143, 0.548], } P < 0.001) \), and high preoperative body temperature \( \text{(OR 0.027 [0.004, 0.164], } P < 0.001) \) were protective against hypothermia; and ASA-PS 2–3 \( \text{(compared with ASA-PS 1; } \text{OR 6.608 [1.138, 38.366], } P = 0.035 \text{ and OR 6.118 [1.509, 24.806], } \text{P } = 0.011, \text{ respectively}) \), long anesthetic duration \( \text{(OR 1.009 [1.003, 1.016], } \text{P } = 0.005 \text{), and high BSA/weight ratio } \text{(OR 1.659 [1.225, 2.247], } \text{P } = 0.001) \) were independent risk factors for intraoperative hypothermia (Fig. 3).

Four variables were included in the severe intraoperative hypothermia model, three of which were independently related to severe intraoperative hypothermia. Upper-extremity warming group \( \text{(OR 0.163 [0.040, 0.673], } \text{P } = 0.012 \text{) and high ambient temperature } \text{(OR 0.432 [0.211, 0.885], } \text{P } = 0.022 \text{) were protective against severe hypothermia, and long anesthetic duration } \text{(OR 1.007 [1.001, 1.013], } \text{P } = 0.028) \text{ was an independent risk factor for severe hypothermia.} \)
vere intraoperative hypothermia (Fig. 3).

**Discussion**

This study demonstrated that forced-air warming using an upper-body blanket prevented perioperative hypothermia more effectively than did warming of the lower body with a blanket during spine surgery in the prone position.

Previous studies have reported that warming the lower body is more effective than warming the upper body for patients in the supine position [9,10]. Motamed et al. [9] reported that lower-body warming resulted in a greater initial redistribution of the core temperature but normothermia was regained more rapidly during major abdominal surgery (120 vs. 180 min). Yamakage et al. [10] reported that lower-body warming below the T10 dermatome was more effective than upper-body warming above the

https://doi.org/10.4097/kja.21087
T7 dermatome in patients receiving spinal anesthesia.

Brauer et al. [4,5] used a Cooper manikin model, and reported that the maximum heat transfer values were 18.3 and 26.6 W with lower- and upper-body blankets, respectively. However, the lower-body blanket covered a larger area (49 W) than the upper-body blanket (37.8 W). The total heat balance was approximately 10 W higher using the lower-body blanket [4,5].

Min et al. [11] reported that upper-body warming was more effective than lower-body warming when the patient was in the lateral decubitus position during thoracoscopic surgery. They attributed this to padding between the legs, which reduced the surface area covered by the lower-body blanket. They also suggested that heat distribution inside the blanket may vary more with a larger lower-body blanket.

In this study, forced-air warming of the upper-body blanket prevented perioperative hypothermia more effectively than did warming of the lower-body blanket, with the patient in the prone position during spine surgery. This result may be explained as follows.

First, the BSA covered by the upper-body blanket was larger, (covering both arms and hands, and the entire trunk above the T4 spinous process level) than that covered by the lower-body blanket. The area covered by the upper-body blanket was similar to that reported by Brauer et al. (~0.35 m²). The lower-body blanket covered both legs and the lower buttocks below the coccyx, but the lower abdomen was not covered (~0.24 m² in the study of Brauer et al.) [4,5]. The major reason for the difference in results between a previous study conducted in the supine position and our study may be that lower-body warming reached up to the T10 dermatome in the previous investigation [10].

Second, heat transfer may be higher with the upper- versus lower-body blanket, as also reported by Brauer et al. [4,5]. They reported that the maximum heat transfer values were 18.3 and 26.6 W using lower- and upper-body blankets, respectively. Min et al. [11] suggested that the larger size of the lower-body blanket might explain the variability in heat distribution and lower efficacy. However, we suggest that the blanket design (upper-body blanket: narrow and long, lower-body blanket: wide and short) and the location of the nozzle access could have been more important in our study because the upper- and lower-body blankets were the same size (208 × 71 cm [14,768 cm²] and 104 × 142 cm [14,768 cm²], respectively).

Third, in the upper-warming group, continuous monitoring and management of blanket inflation was better performed, because the forced-air warmer was located close to the anesthesiologist. However, in the lower-warming group, the warming blanket was remote from the anesthesiologist and the entire blanket was covered by a surgical drape, making monitoring and management of blanket inflation relatively difficult. In addition, although the surgeon was aware of the lower-warming, surgical instruments were often placed on the lower-body blanket during the spine surgery; this could explain the variable heat distribution. This may have affected the results of this study.

Fourth, the difference in distance between the warming and measurement sites may have affected the results. We took the nasopharyngeal temperature as the intraoperative core temperature; the nasopharyngeal temperature is more reliable than the bladder temperature because the latter is strongly influenced by urine flow [16,17]. An esophageal probe may be misplaced due to the relatively long distance from the incisor (approximately 40 cm) compared to a nasopharyngeal probe [14,18–20]. However, the upper-body blanket and nasopharynx are closer together compared with the nasopharynx and lower-body blanket, which could raise the nasopharyngeal temperature more quickly, even though the head was not covered with the upper-body blanket in our study. Further studies evaluating the effect on the temperature measurement site of the warming site are needed.

One study reported on the differences between upper- and lower-body blanket warming during spine surgery in the prone position. Buraimoh et al. [12] reported no difference in warming efficacy between upper- and lower-body blankets in patients undergoing spine surgery. In their study, the incidence rates of severe hypothermia (< 35°C) and mild to moderate hypothermia (35–36°C) in the upper-warming group were similar to those in our study (18.4% and 34.2%, respectively), but the rates of severe and mild to moderate hypothermia in the lower-warming group were lower than our rates (11.1% and 30.6%, respectively). This was probably because the BSA covered by the lower-body warming blanket used in the previous study (an underbody warming blanket that covered the torso and legs) was larger than in our study. In addition, the use of bladder temperature might have affected the results. Forced-air warming underbody blankets have been shown to be effective, but are more expensive than conventional warming devices and so are not particularly popular [8]. Our findings may help with blanket selection.

Reduced perioperative complications and enhanced patient satisfaction due to the lower incidence of hypothermia were not confirmed in our upper-warming group because of the low power of the study. The lack of any differences in intraoperative blood loss and the transfusion requirement may have been partially influenced by the minimally invasive surgery that was performed. The lack of any differences in postoperative shivering, thermal discomfort, and patient satisfaction may have been due to the continuous full-body warming in the PACU in both groups.
In our study, heat redistribution within the first hour was greater than that in a previous study of spine surgery patients [21]. Differences in participant characteristics and warming blankets may explain this result. We included only patients undergoing thoracolumbar spine surgery, in whom the center of the body is more widely exposed, while the previous study included cervical spine surgical patients who were warmed using a full-body blanket or spine-specific blanket [21]. The long unwarmed period (38 min) in our study could explain the greater decrease in core temperature.

Our results show that a higher ASA-PS, lower preoperative body temperature, and large surface area to body mass ratio were independent risk factors for intraoperative hypothermia. The effect of a low preoperative body temperature has been reported in previous studies [22,23]. The effect of a large surface area to body mass ratio on thermoregulation and the relationship between the surface area to body mass and ambient temperature have been documented [24]. Therefore, it is intuitive that a large surface area to body mass ratio was an independent risk factor for intraoperative hypothermia in this study. A long anesthetic duration and low ambient temperature were independent risk factors for intraoperative hypothermia and severe intraoperative hypothermia, consistent with previous studies [22,23]. Therefore, we suggest that a high ambient temperature can prevent severe hypothermia, and additional warming effort is required if anesthesia of long duration is anticipated.

This study had some limitations. First, the tympanic temperature was measured to help reduce discomfort in conscious patients, but the pre- and post-operative tympanic temperatures can differ from the intraoperative nasopharyngeal temperature. Nevertheless, tympanic temperature is the most accurate and precise peripheral temperature measurement [13]. Second, for the reasons mentioned above, the nasopharyngeal temperature was taken as the core temperature in our study [16]. We placed the nasopharyngeal temperature probe at a depth of 9–10 cm in the nasopharynx based on a previous imaging study, and the probe was fixed with tape so that its position did not change [14]. However, the prone position could have resulted in changes in the probe position and nasal secretions. Third, the results may not be informative regarding the effect of the level, location, or type of spine surgery, because the patients showed no differences in surgical characteristics. Also, the results may not generalize to patients undergoing major thoracolumbar spine surgery, as most of our patients underwent spine surgery below level 2. Further studies examining additional surgical factors are required. Fourth, no follow-up was performed, so long-term complications are unknown. Randomized controlled trials including larger samples and evaluating long-term complications of mild perioperative hypothermia are required.

In conclusion, upper-body blanket warming was more effective than lower-body blanket warming to prevent perioperative hypothermia during thoracolumbar spine surgery in the prone position.

Funding

None.

Conflicts of Interest

All authors have no potential conflicts of interests. The data used in this study is available by request to the corresponding author. Due to protection of sensitive patient data, the data used are not publicly available.

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Jae-Hwa Yoo (Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing)
Si Young Ok (Conceptualization; Writing – review & editing)
Sang Ho Kim (Formal analysis)
Ji Won Chung (Formal analysis)
Sun Young Park (Formal analysis)
Mun Gyu Kim (Investigation)
Ho Bum Cho (Investigation)
Sang Hoon Song (Investigation)
Yun Jeong Choi (Investigation)
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References

The impact of preoperative glycated hemoglobin (HbA1c) on postoperative complications after elective major abdominal surgery: a meta-analysis

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Background: Diabetes is a risk factor for postoperative complications. Previous meta-analyses have shown that elevated glycated hemoglobin (HbA1c) levels are associated with postoperative complications in various surgical populations. However, this is the first meta-analysis to investigate the association between preoperative HbA1c levels and postoperative complications in patients undergoing elective major abdominal surgery.

Methods: PRISMA guidelines were adhered to for this study. Six databases were searched up to April 1, 2020. Primary studies investigating the effect of HbA1c levels on postoperative complications after elective major abdominal surgery were included. Risk of bias and quality of evidence assessments were performed. Data were pooled using a random effects model. Meta-regression was performed to evaluate different HbA1c cut-off values.

Results: Twelve observational studies (25,036 patients) were included. Most studies received a ‘good’ and ‘moderate quality’ score using the NOS and GRADE, respectively. Patients with a high HbA1c had a greater risk of anastomotic leaks (odds ratio [OR]: 2.80, 95% CI [1.63, 4.83], P < 0.001), wound infections (OR: 1.21, 95% CI [1.08, 1.36], P = 0.001), major complications defined as Clavien-Dindo [CD] 3–5 (OR: 2.16, 95% CI [1.54, 3.01], P < 0.001), and overall complications defined as CD 1–5 (OR: 2.12, 95% CI [1.48, 3.04], P < 0.001).

Conclusions: An HbA1c between 6% and 7% is associated with higher risks of anastomotic leaks, wound infections, major complications, and overall postoperative complications. Therefore, guidelines with an HbA1c threshold > 7% may be putting pre-optimized patients at risk. Future randomized controlled trials are needed to explore causation before policy changes are made.

Keywords: Diabetes mellitus; Elective surgical procedures; General surgery; Glycated hemoglobin A; Operative surgical procedures; Postoperative complications.

Introduction

Diabetes mellitus is known to be a predisposing risk factor for postoperative complications, such as infections, poor wound healing, anastomotic leaks, and cardiac complications. Compared with non-diabetic patients, both in-hospital and long-term mortality rates are considerably higher in patients with diabetes [1]. Hence, glycemic control during the perioperative period could be a modifiable risk factor and a potential target for reduc-
ing postoperative complications.

The American Diabetes Association endorses the use of glycated hemoglobin (HbA1c) levels to monitor glycemic control in patients with diabetes [2]. This is a measure that reflects the average blood glucose level over a three-month period, providing an indirect measurement of how effectively blood glucose is controlled. Systematic reviews and meta-analyses have shown that increased levels of preoperative HbA1c are associated with higher rates of postoperative complications and poorer outcomes in surgical specialties, such as cardiothoracic [3], bariatric [4], and orthopedic surgery [5].

Major abdominal surgery, defined as a major operation involving the abdominal and/or retroperitoneal compartment, is associated with high postoperative morbidity due to the extensive nature of the surgery. Despite the clinical significance of this, no previous systematic review or meta-analysis has investigated the association between preoperative HbA1c levels and postoperative complications in this population. Furthermore, there is no consensus on the HbA1c threshold at which it would be advisable to postpone elective surgery. The Joint British Diabetes Societies for Inpatient Care and the Association of Anesthetists of Great Britain and Ireland recommend further optimization of glycemic control at an HbA1c threshold of 8.5% [6], while the US Society for Ambulatory Anesthesia recommends a threshold of 7.0% [7], and the Australian Diabetes Society recommends a threshold of 9.0% [8]. An HbA1c target set too low may be unrealistic and may delay a patient’s surgery unnecessarily, whereas an HbA1c target set too high may be inadequate in risk prognostication and in reducing postoperative complications.

Thus, there is a gap in the literature regarding the association between preoperative HbA1c levels and postoperative complications after elective major abdominal surgery despite the increasing incidence of both diabetes and abdominal surgery. The UK National Diabetes Inpatient Audit found that 21% of all surgical patients have diabetes, and general surgery (36%) and colorectal surgery (22%) are the surgical specialties with the highest prevalence [9]. Greater understanding of the association between preoperative HbA1c levels and postoperative complications after elective major abdominal surgery could therefore help with risk prognostication and perioperative management.

This is the first meta-analysis to evaluate all the available evidence regarding the association between preoperative HbA1c levels and postoperative complications in the unique population of patients undergoing elective major abdominal surgery. Furthermore, we investigated whether a threshold HbA1c level could be used to predict an increase in postoperative complications. The findings from this meta-analysis could have implications for policies in various countries, as different HbA1c cut-off thresholds are currently being used in clinical practice.

Materials and Methods

This meta-analysis has been reported in line with the PRISMA guidelines [10] and registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO, no. CRD 42020167347) [11]. A full description of the methodology has been described previously [12].

Search strategy

The following electronic databases were searched using the search strategy described in Supplementary Digital Content 1, from each database’s earliest record up to April 1, 2020: PubMed, Embase, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and China Knowledge Resource Integrated Database (CNKI).

Study selection

The study selection was performed by two independent reviewers (JKLW and YK). Discrepancies were resolved by a third reviewer (HRA). The eligibility criteria were as follows: randomized controlled trials (RCTs) and observational studies investigating the association between HbA1c levels and postoperative complications by reporting outcomes in at least two HbA1c groups in adult patients undergoing major abdominal surgery. Studies on patients undergoing bariatric, total pancreatectomy, pediatric, emergency, and transplant surgery were excluded [12].

Data collection

Data extraction was performed by two independent reviewers (JKLW and YK) and stored in proformas. The extracted data included study characteristics (author, year, country, study design, type of surgery), patient demographics (age, sex, sample size), intervention and comparator data (HbA1c cut-off value), and outcome data (postoperative complications including major, overall, gastrointestinal, infectious, cardiopulmonary, and renal complications), which were guided by the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) [13]. An exhaustive list of the extracted data items has been published previously [12]. The raw outcomes for each HbA1c level group were extracted and estimates of effects using the methods recommended by the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0.17) were calculated.
Risk of bias and quality of evidence assessment

The risk of bias for the non-randomized observational studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) [14] and converted to the Agency for Healthcare Research and Quality (AHRQ) standards (Supplementary Digital Content 2). The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach was used to grade the quality of evidence as recommended by Cochrane [15].

Data synthesis and statistical analysis

The primary and secondary aims of this meta-analysis were to investigate the associations between preoperative HbA1c levels and major and overall postoperative complications, respectively, where major complications were defined as those fulfilling the Clavien-Dindo (CD) classification grades 3–5, and overall complications were defined as those fulfilling the CD grades 1–5 [16]. Table 1 provides detailed information on the definitions of the CD classification grades 1 through 5. The corresponding primary and secondary outcomes were represented as the odds ratios (ORs) of postoperative complication events between the normal and elevated HbA1c groups.

The postoperative complications extracted from the primary studies were initially graded according to the CD classification, and then grouped according to either the primary outcome (major postoperative complications) or secondary outcome (overall postoperative complications) analyses. Examples of postoperative complications that were included as major postoperative complications (primary outcome) include reoperation [17], anastomotic leak [18–23], 30-day mortality, [23] and major complications fulfilling the CD grades 3–5 [24–26]. Examples of secondary outcomes (overall complications) include anastomotic leak, postoperative ileus, overall infections, wound infections, pneumonia, sepsis, cardiopulmonary complications, and renal failure [13]. The primary and secondary outcomes were quantitatively analyzed. Qualitative analyses were conducted for outcomes reported by two or fewer studies.

Statistical analyses were performed using Stata (2019. Stata Statistical Software: Release 16. StataCorp LLC. StataCorp.). Funnel plots, Begg’s rank correlation tests, and Egger’s regression asymmetry tests were used to assess publication bias [27]. The Duval and Tweedie nonparametric trim and fill method to account for publication bias was performed to formalize the use of funnel plots and adjust the meta-analysis by incorporating theoretical missing trials [27]. The Q-statistic was used to investigate the heterogeneity between the studies. One limitation of Cochrane’s Q-test is that it might be underpowered when studies in a meta-analysis have small sample sizes or low event rates. Therefore, Cochrane recommends that a higher standard be adopted to determine whether there is indeed no significant heterogeneity between the studies. Hence, a higher P value of 0.1 was used rather than the conventional 0.05 [28]. The I² statistical test [29] was carried out to describe the proportion of total variation caused by heterogeneity [30]. An I² < 30% was considered mild heterogeneity, > 50% as notable heterogeneity, and anything between 30% and 50% as moderate heterogeneity. However, these must be interpreted with caution, as inconsistency may not necessarily be important with low I² values because the importance of the I² value depends on the magnitude and direction of effects, strength of evi-

Table 1. Clavien-Dindo Classification Definitions

<table>
<thead>
<tr>
<th>Grades</th>
<th>Definition [16]</th>
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<tbody>
<tr>
<td>I</td>
<td>Any deviation from normal postoperative course without need for pharmacological treatment or surgical, endoscopic, or radiological interventions</td>
</tr>
<tr>
<td></td>
<td>Allowed therapeutic regimens: antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy</td>
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<tr>
<td></td>
<td>This grade also includes wound infections opened at the bedside</td>
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<tr>
<td>II</td>
<td>Requiring pharmacological treatment with drugs other than those included in the grade I complications</td>
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<tr>
<td></td>
<td>Also includes blood transfusions and total parenteral nutrition</td>
</tr>
<tr>
<td>III</td>
<td>Requiring surgical, endoscopic, or radiological interventions</td>
</tr>
<tr>
<td></td>
<td>a: Not under general anesthesia</td>
</tr>
<tr>
<td></td>
<td>b: Under general anesthesia</td>
</tr>
<tr>
<td>IV</td>
<td>Life-threatening complication (including central nervous system complications)* requiring intensive care unit management</td>
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<tr>
<td></td>
<td>a: Single organ dysfunction (including dialysis)</td>
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<td></td>
<td>b: Multi-organ dysfunction</td>
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<td>V</td>
<td>Death</td>
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</tbody>
</table>

*Including brain hemorrhage, ischemic stroke, or subarachnoid bleeding but excluding transient ischemic attacks.
dence for heterogeneity including the P value from the chi-squared test, and/or the confidence interval for $I^2$ [28]. The random effects model (DerSimonian–Laird) was used to derive pool estimates to account for inter-study heterogeneity. A meta-regression was performed to evaluate the effect that different HbA1c cut-off values had on the following outcomes: major postoperative complications, overall postoperative complications, anastomotic leak, overall infections, and wound infections.

**Ethics approval and consent to participate**

No ethics approval or consent to participate was required, as only secondary data were used.

**Results**

**Search results**

The search yielded 2,539 records. One additional record was identified through a manual search of the bibliographies. Fifteen and twelve records met the criteria for qualitative and quantitative analyses, respectively (Fig. 1). The following three records were not included in the quantitative analysis: the study by Lee et al. [31] because it was the only study that used the outcome measures progression-free survival, cancer specific survival, and overall survival and hence could not be combined with other studies; the study by Goh et al. [25] because the authors used an HbA1c cut-off value of 8.0%, which was higher than the cut-off values used in other studies and would have confounded the quantitative analysis; and the study by Zhang [32] because the number of patients in each HbA1c level group was not reported in the study.

**Study characteristics**

The study characteristics are summarized in Table 2. All the studies were conducted between 2008 and 2019. Eleven studies were conducted in Asia, two in the USA [24,33], and two in Europe [18,26]. There were no RCTs that met our inclusion criteria. Twelve studies were performed retrospectively and three employed a prospective design [18,24,26], where patients were followed up from two months [26] to four years [24]. Most studies included gastrointestinal (GI) tract surgeries [17,18,20–26,33–35], though one included esophagectomies [19], one included GI tract and hepatopancreato-biliary surgeries [26], one included exclusively biliary surgeries [32], one included genitourinary surgeries [24], and one included exclusively genitourinary surgeries [31]. The HbA1c cut-off values used in the studies to dichotomize the case and control groups were variable. The most common cut-off values were 6.5%, which were used by five studies [19,24,26,33,34], and 7.0%, which was used in four studies [17,20,23,32]. Most studies used HbA1c levels taken within 3 months of the surgery, while one study used HbA1c levels taken within 6 months of the surgery [31]. Additionally, a few studies did not state the time-frame between the HbA1c measurements and the surgery [17,20–23,32,34]. A total of 25,036 patients were included in the quantitative analysis.

The most studied outcomes were infections [17,18,20,22,23,32,33] and anastomotic leaks [18–23,32]. Some studies investigated the individual effects of different types of infections, such as pneumonia, urinary tract infections, wound infections, and sepsis [17,18,23,33], while others only investigated the collective effect of all infections [20,22,32]. A few studies only investigated total postoperative complications according to the CD classification [24–26].

**Risk of bias and quality of evidence assessment**

According to the risk of bias assessment, all studies scored at least a 7/9 on the NOS, which equates to a “good quality” score af-
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Type of surgery</th>
<th>Sample size, n</th>
<th>HbA1c cut-off (no. of patients, percentage)</th>
<th>Time window between HbA1c level result and surgery</th>
<th>Outcome measures</th>
</tr>
</thead>
</table>
| Lee et al. 2015 [31]         | South Korea | Retrospective | Nephrectomy (radical and partial) for renal cell carcinoma                      | n = 3075       | ≥ 6.8% (n = 158, 50%) < 6.8% (n = 158, 50%) | Within 6 months of the surgery                    | • Progression-free survival  
  • Cancer specific survival  
  • Overall survival                                                                   |
| Gustafsson et al. 2009 [18]  | Sweden      | Prospective  | Elective colorectal resection (including cancer, inflammatory bowel disease, benign pathology) | n = 120        | > 6.0% (n = 31, 25.8%) ≤ 6.0% (n = 89, 74.2%) | 1 day before surgery                                | • Postoperative glucose control  
  • Magnitude of inflammatory response  
  • Postoperative recovery  
  • 30-day overall morbidity                                                              |
| Goh et al. 2017 [25]         | Singapore   | Retrospective | Colorectal surgery                                                              | n = 149        | ≥ 8% (n = 31, 23.8%) < 8% (n = 99, 76.2%)   | Within 3 months of the surgery                     | • Postoperative complications (CD grade 2 and above)                               |
| Goodenough et al. 2015 [24]  | USA         | Prospective  | *Abdominal surgery                                                              | n = 1017       | ≥ 6.5% (n = 183, 41.8%) < 6.5% (n = 255, 52.8%) | Within 3 months of the surgery                     | • Primary: Major complication  
  CD grade 3–5 within 30 days  
  • Secondary: Any complication, including CD grade 1–2  
  • Primary: 30-day complications defined by CD  
  • Secondary: Major complications 30-day readmission rates, postoperative care setting |
| Kamarajah et al. 2018 [26]   | UK          | Prospective  | Gastrointestinal and hepatobiliary surgery                                       | n = 381        | ≥ 6.5% (n = 49, 27.1%) < 6.5% (n = 132, 72.9%) | Within 3 months of the surgery                     | • Primary: Any post-operative complication  
  Length of hospital stay  
  • 30-day and 180-day mortality rates  
  • Postoperative complications (wound infection, pneumonia, urinary tract infection, sepsis)  
  • Post-discharge outcomes (readmission within 14 d, readmission within 30 d) |
| Huang et al. 2017 [25]       | China       | Retrospective | Surgical resection for gastrointestinal cancer                                   | n = 209        | ≥ 7% (n = 67, 56.8%) < 7% (n = 51, 43.2%)   | Not stated                                         |                                                                                  |
| Jones et al. 2017 [33]       | USA         | Retrospective | Gastrointestinal surgery                                                        | n = 21541      | > 6.5% (n = 8822, 41.0%)  
  5.7–6.5% (n = 8118, 37.7%)  
  5.7% (n = 4601, 21.4%) | Within 3 months of the surgery                                                        | • Any post-operative complication  
  • Infectious complications (wound infection, pneumonia, urinary tract infection, sepsis)  
  • Post-discharge outcomes (readmission within 14 d, readmission within 30 d) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
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<th>Time window between HbA1c level result and surgery</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villamiel et al.</td>
<td>Philippines</td>
<td>Retrospective</td>
<td>Elective colorectal surgery</td>
<td>n = 157</td>
<td>&gt; 7% (n = 15, 34.1%) ≤ 7% (n = 29, 65.9%)</td>
<td>Not stated</td>
<td>· Primary: Length of hospital stay</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>· Secondary: Discharge within 30 postoperative days, postoperative complications, reoperation, pneumonia, wound infection</td>
</tr>
<tr>
<td>Okamura et al.</td>
<td>Japan</td>
<td>Retrospective</td>
<td>Esophagectomy for esophageal cancer</td>
<td>n = 300</td>
<td>≥ 6.5% (n = 27, 9%) 6.0–6.4% (n = 50, 16.7%) ≤ 6.0% (n = 223, 74.3%)</td>
<td>Within 3 months of the surgery</td>
<td>· Anastomotic leak</td>
</tr>
<tr>
<td>Oh et al. 2018</td>
<td>South Korea</td>
<td>Retrospective</td>
<td>Elective major laparoscopic abdominal surgery</td>
<td>n = 1885</td>
<td>≥ 6.0% (n = 628, 33.3%) ≤ 6.0% (n = 1257, 66.7%)</td>
<td>Within 1 month of the surgery</td>
<td>· Acute kidney injury (postoperative day 0–3, stage 1–3)</td>
</tr>
<tr>
<td>Chen et al. 2018</td>
<td>China</td>
<td>Retrospective</td>
<td>Colorectal surgery</td>
<td>n = 126</td>
<td>≥ 6.3% (n = 67, 53.2%) ≤ 6.3% (n = 59, 46.8%)</td>
<td>Not stated</td>
<td>· Anastomotic leak</td>
</tr>
<tr>
<td>Zhou et al. 2019</td>
<td>China</td>
<td>Retrospective</td>
<td>Colorectal and upper gastrointestinal surgery</td>
<td>n = 118</td>
<td>7–8% (n = 27, 22.9%) 6.5 ≤ 7% (n = 27, 22.9%) 5.7 ≤ 6.5% (n = 34, 28.8%) &lt; 5.7% (n = 30, 25.4%)</td>
<td>Not stated</td>
<td>· Postoperative delirium</td>
</tr>
<tr>
<td>Dai et al. 2017</td>
<td>China</td>
<td>Retrospective</td>
<td>Colorectal surgery</td>
<td>n = 201</td>
<td>&gt; 7% (n = 112, 55.7%) ≤ 7% (n = 89, 44.3%)</td>
<td>Not stated</td>
<td>· Anastomotic leak</td>
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<tr>
<td></td>
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<td>· Length of stay</td>
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<td>· Duration of surgery</td>
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<td></td>
<td></td>
<td>· Major intra-operative bleeding</td>
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<td></td>
<td></td>
<td>· Infections</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>· Acute myocardial infarction</td>
</tr>
<tr>
<td>Zhang et al. 2008</td>
<td>China</td>
<td>Retrospective</td>
<td>Cholecystectomy</td>
<td>n = 86</td>
<td>&gt; 7.0 ≤ 7.0</td>
<td>Not stated</td>
<td>· Anastomotic leak</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Number of patients per group not reported</td>
<td></td>
<td>· Infections</td>
</tr>
<tr>
<td>Wang et al. 2010</td>
<td>China</td>
<td>Retrospective</td>
<td>Gastrointestinal tumor surgery</td>
<td>n = 82</td>
<td>&lt; 6.2 (n = 47, 79.7%) ≥ 6.2 (n = 35, 42.7%)</td>
<td>Not stated</td>
<td>· Bloating</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>· Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>· Anastomotic leak</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>· Time to flatus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>· Length of hospital stay</td>
</tr>
</tbody>
</table>

* Included four gynecological procedures that constituted only 0.7% of the total number of surgeries.
Major postoperative complications

Nine studies were included in this analysis [17–24,26]. Neither Begg’s rank correlation test (P = 0.175) nor Egger’s regression asymmetry test (P = 0.565) showed significant publication bias in our meta-analysis, which was consistent with the funnel plots (Supplementary Digital Content 4). Neither the Q-statistic nor the I²-statistic showed heterogeneity among the included studies (P = 0.711, I² = 0%). The pooled results showed that the patients with an elevated HbA1c level tended to have a higher risk of developing major complications after surgery (OR: 2.16, 95% CI [1.54, 3.01], P < 0.001) (Fig. 2).

Overall postoperative complications

Among the 12 studies reporting overall complications [17–24,26,33–35], Wang et al. [22] reported on anastomotic leak and postoperative infection data separately. We included this study in our primary analysis and conducted a sensitivity analysis with the excluded study to ensure that patients with complications were not counted twice, as we were unable to obtain the original patient-level data from the authors.

For the primary analysis, with Wang et al.’s postoperative infection data included [22], Egger’s test for small-study effects found significant publication bias (P = 0.001), which was consistent with the funnel plots (Supplementary Digital Content 5). The Q-statistic and I²-statistic results showed heterogeneity among the studies (P < 0.001, I² = 75.6%). Pooled results showed that patients with an elevated HbA1c level tended to have a higher risk of developing overall complications (CD grade ≥ 1) after surgery (OR: 2.12, 95% CI [1.48, 3.04], P < 0.001) (Fig. 3). The Duval and Tweedie nonparametric trim and fill method adopted to adjust for publication bias, and the meta-analysis using the trim and fill method resulted in similar conclusions. The sensitivity analysis also showed similar conclusions (OR: 2.00, 95% CI [1.41, 2.85]). The funnel and forest plots are shown in Supplementary Digital Content 6.

Gastrointestinal complications

Anastomotic leak

Six studies were included in this analysis [18–23]. No significant publication bias was found using Egger’s test for small-study effects (P = 0.401) or Begg’s rank correlation test (P = 0.452) (Supplementary Digital Content 7). Neither the Q-statistic nor the I²-statistic showed heterogeneity among the studies (P = 0.711, I² = 0%). The pooled results showed that patients with an elevated HbA1c level tended to have a higher risk of developing an anastomotic leak after surgery (OR: 2.80, 95% CI [1.63, 4.83], P < 0.001) (Fig. 4). The Duval and Tweedie nonparametric trim and fill method adopted to adjust for publication bias, and the meta-analysis using the trim and fill method resulted in similar conclusions. The sensitivity analysis also showed similar conclusions (OR: 2.32, 95% CI [1.41, 3.81]). The funnel and forest plots are shown in Supplementary Digital Content 8.
Fig. 2. Forest plot of the effect of HbA1c level on major postoperative complications (P < 0.001).

<table>
<thead>
<tr>
<th>Study</th>
<th>Elevated HbA1c Events</th>
<th>Elevated HbA1c Total</th>
<th>Normal HbA1c Events</th>
<th>Normal HbA1c Total</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustafsson 2009</td>
<td>1</td>
<td>31</td>
<td>2</td>
<td>89</td>
<td>1.45</td>
<td>1.16</td>
<td>1.63</td>
<td>0.2346</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>4</td>
<td>35</td>
<td>5</td>
<td>47</td>
<td>1.08</td>
<td>1.06</td>
<td>1.06</td>
<td>0.27</td>
</tr>
<tr>
<td>Chen 2018</td>
<td>15</td>
<td>67</td>
<td>5</td>
<td>59</td>
<td>3.12</td>
<td>3.10</td>
<td>3.10</td>
<td>0.87</td>
</tr>
<tr>
<td>Goodenough 2015</td>
<td>53</td>
<td>183</td>
<td>43</td>
<td>255</td>
<td>2.01</td>
<td>2.01</td>
<td>2.01</td>
<td>0.87</td>
</tr>
<tr>
<td>Kamarajah 2018</td>
<td>3</td>
<td>49</td>
<td>7</td>
<td>132</td>
<td>1.16</td>
<td>1.16</td>
<td>1.16</td>
<td>0.75</td>
</tr>
<tr>
<td>Okamura 2017</td>
<td>8</td>
<td>27</td>
<td>27</td>
<td>273</td>
<td>3.84</td>
<td>3.84</td>
<td>3.84</td>
<td>0.72</td>
</tr>
<tr>
<td>Dai 2017</td>
<td>12</td>
<td>112</td>
<td>3</td>
<td>89</td>
<td>3.44</td>
<td>3.44</td>
<td>3.44</td>
<td>0.63</td>
</tr>
<tr>
<td>Huang 2017</td>
<td>3</td>
<td>67</td>
<td>1</td>
<td>51</td>
<td>2.34</td>
<td>2.34</td>
<td>2.34</td>
<td>0.23</td>
</tr>
<tr>
<td>Villamiel 2019</td>
<td>1</td>
<td>15</td>
<td>3</td>
<td>29</td>
<td>0.62</td>
<td>0.62</td>
<td>0.62</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Fixed effect model: 586 of 1,024 events
Random effects model: 2.16 [1.54, 3.01] 100.0%

Heterogeneity: Heterogeneity: $\hat{I}^2 = 0\%$, $\tau^2 = 0$, $P = 0.71$

Favours Elevated HbA1c  Favours Normal HbA1c

Fig. 3. Forest plot of the effect of HbA1c level on overall complications (P < 0.001).

<table>
<thead>
<tr>
<th>Study</th>
<th>Elevated HbA1c Events</th>
<th>Elevated HbA1c Total</th>
<th>Normal HbA1c Events</th>
<th>Normal HbA1c Total</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustafsson 2009</td>
<td>16</td>
<td>31</td>
<td>26</td>
<td>89</td>
<td>2.58</td>
<td>2.58</td>
<td>2.58</td>
<td>0.3%</td>
</tr>
<tr>
<td>Oh 2018</td>
<td>28</td>
<td>628</td>
<td>41</td>
<td>1,257</td>
<td>1.38</td>
<td>1.38</td>
<td>1.38</td>
<td>1.2%</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>11</td>
<td>35</td>
<td>6</td>
<td>47</td>
<td>3.13</td>
<td>3.13</td>
<td>3.13</td>
<td>0.2%</td>
</tr>
<tr>
<td>Chen 2018</td>
<td>15</td>
<td>67</td>
<td>5</td>
<td>59</td>
<td>3.12</td>
<td>3.12</td>
<td>3.12</td>
<td>0.2%</td>
</tr>
<tr>
<td>Goodenough 2015</td>
<td>53</td>
<td>183</td>
<td>43</td>
<td>255</td>
<td>2.01</td>
<td>2.01</td>
<td>2.01</td>
<td>1.2%</td>
</tr>
<tr>
<td>Jones 2017</td>
<td>2,683</td>
<td>8,822</td>
<td>3,594</td>
<td>12,719</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
<td>95.2%</td>
</tr>
<tr>
<td>Kamarajah 2018</td>
<td>31</td>
<td>49</td>
<td>61</td>
<td>132</td>
<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
<td>0.6%</td>
</tr>
<tr>
<td>Okamura 2017</td>
<td>8</td>
<td>27</td>
<td>27</td>
<td>273</td>
<td>3.84</td>
<td>3.84</td>
<td>3.84</td>
<td>0.2%</td>
</tr>
<tr>
<td>Dai 2017</td>
<td>41</td>
<td>112</td>
<td>12</td>
<td>89</td>
<td>3.71</td>
<td>3.71</td>
<td>3.71</td>
<td>0.4%</td>
</tr>
<tr>
<td>Huang 2017</td>
<td>18</td>
<td>67</td>
<td>8</td>
<td>51</td>
<td>1.97</td>
<td>1.97</td>
<td>1.97</td>
<td>0.3%</td>
</tr>
<tr>
<td>Villamiel 2019</td>
<td>4</td>
<td>15</td>
<td>10</td>
<td>29</td>
<td>0.69</td>
<td>0.69</td>
<td>0.69</td>
<td>0.2%</td>
</tr>
<tr>
<td>Zhou 2019</td>
<td>13</td>
<td>27</td>
<td>4</td>
<td>30</td>
<td>6.04</td>
<td>6.04</td>
<td>6.04</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Fixed effect model: 10,063 of 15,030 events
Random effects model: 2.12 [1.48, 3.04] 100.0%

Heterogeneity: $\hat{I}^2 = 76\%$, $\tau^2 = 0.2346$, $P < 0.01$

Favours Elevated HbA1c  Favours Normal HbA1c

tistic showed significant heterogeneity between the studies ($P = 0.600, \hat{I}^2 = 0\%$). Pooled results showed that patients with elevated HbA1c levels tended to have a higher risk of developing anastomotic leaks (OR: 2.80, 95% CI [1.63, 4.83], $P < 0.001$) (Fig. 4).

**Postoperative ileus**

Only two studies investigated the impact of HbA1c levels on postoperative ileus [18,23]. Gustafsson et al. [18] found that the rate of events was 9.7% in the HbA1c level > 6% group and 1.1%
in the HbA1c level ≤ 6% group. Although the rate of events in the HbA1c level > 6% group was higher, the significance was not reported. When an HbA1c cut-off of 7% was used, Huang et al. [23] found no difference in the rate of postoperative ileus between the HbA1c groups (P = 0.284).

### Infectious complications

#### Overall infections

This analysis included six studies [17,18,20,22,23,33]. Egger’s test for small-study effects found significant publication bias (P = 0.038) (Supplementary Digital Content 8). Although the Q-statistic did not show significant heterogeneity among studies (P = 0.113), the I²-statistic found moderate heterogeneity (I² = 43.8%). The pooled results showed that patients with an elevated HbA1c level tended to have a higher risk of developing infections (OR: 1.69, 95% CI [1.05, 2.71]) (Fig. 5). However, the meta-analysis using the trim and fill method showed this effect to be insignificant (OR: 1.18, 95% CI [0.77, 1.82]).

#### Wound infection

Three studies were included in this analysis [18,23,33]. No significant publication bias was found using either Egger’s test for small-study effects (P = 0.947) or Begg’s rank correlation test (P = 1.000). However, the funnel plot showed different results (Supplementary Digital Content 9). No significant heterogeneity was found among the studies using either the Q-statistic nor the I²-statistic (P = 0.757, I² = 0%). Pooled results showed that patients with an elevated HbA1c level tended to have a higher risk of developing wound infections (OR: 1.21, 95% CI [1.08, 1.36], P = 0.001) (Fig. 6). The meta-analysis using the trim and fill method did not alter this conclusion.

#### Pneumonia

Four studies were included in this analysis [17,18,23,33]. No significant publication bias was found using Egger’s test for small-study effects (P = 0.385) or Begg’s rank correlation test (P = 1.000) in our meta-analysis. However, the funnel plots showed different results. No significant heterogeneity between the studies was found using the Q-statistic or the I²-statistic (P = 0.424, I² = 0%). The pooled results showed that patients with an elevated HbA1c level tended to have a lower risk of developing pneumonia after surgery (OR: 0.77, 95% CI [0.61, 0.97]). However, this effect became insignificant (OR: 0.74, 95% CI [0.44, 1.25], P = 0.026) when the trim and fill method was used to adjust for publication bias (Supplementary Digital Content 10).

#### Sepsis

Only two studies reported outcomes on postoperative sepsis [18,33]. Gustafsson et al. [18] found an event rate of 0% in the HbA1c level > 6% group and 1.1% in the HbA1c level ≤ 6% group. However, the significance was not reported. Jones et al. [33] used three HbA1c cut-off values: < 5.7%, 5.7–6.4% and ≥ 6.5%. There was no significant difference in the event rates between the three groups (P = 0.80). Using the HbA1c level < 5.7% group as the reference group, no differences in the adjusted OR were found between any of the groups in either study.

### Cardiopulmonary complications

Only two studies reported cardiopulmonary complications [18,20]. Although the complication rates for respiratory failure,

<table>
<thead>
<tr>
<th>Study</th>
<th>Elevated HbA1c Events</th>
<th>Normal HbA1c Events</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95% CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustafsson 2009</td>
<td>0</td>
<td>2</td>
<td>0.56</td>
<td>0.03</td>
<td>11.89</td>
<td>8.0%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Huang 2017</td>
<td>3</td>
<td>0</td>
<td>5.59</td>
<td>0.28</td>
<td>110.67</td>
<td>3.3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Okamura 2017</td>
<td>8</td>
<td>27</td>
<td>3.84</td>
<td>1.53</td>
<td>9.59</td>
<td>21.2%</td>
<td>35.3%</td>
</tr>
<tr>
<td>Chen 2018</td>
<td>15</td>
<td>67</td>
<td>3.12</td>
<td>1.06</td>
<td>9.19</td>
<td>25.6%</td>
<td>25.4%</td>
</tr>
<tr>
<td>Dai 2017</td>
<td>12</td>
<td>112</td>
<td>3.44</td>
<td>0.94</td>
<td>12.59</td>
<td>18.5%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>4</td>
<td>35</td>
<td>1.08</td>
<td>0.27</td>
<td>4.37</td>
<td>23.4%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>339</td>
<td>608</td>
<td>2.73</td>
<td>1.59</td>
<td>4.68</td>
<td>100.0%</td>
<td>--</td>
</tr>
<tr>
<td>Random effects model</td>
<td>2.80</td>
<td>1.63</td>
<td>4.83</td>
<td>100.0%</td>
<td>--</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4. Forest plot of the effect of HbA1c level on anastomotic leak (P < 0.001).
pleural fluid, cardiac failure, and cardiac arrhythmia were reported, no P values were reported by Gustafsson et al. [18] For acute myocardial infarctions, Dai et al. [20] reported an event rate of 8% in the HbA1c level > 7% group and 2.2% in the HbA1c level < 7% group (P < 0.05).

Renal complications

Only one study reported acute kidney injury (AKI) events postoperatively. Oh et al. [35] measured the association between an HbA1c cut-off value of 6% and the AKI stage (The Kidney Disease: Improving Global Outcomes or KDIGO staging) and the total number of AKI events. There was no difference for any of the AKI stages between the groups with an HbA1c level < 6% or ≥ 6% (P > 0.05). Similarly, for the total number of AKI events, there was no difference between the groups (OR: 1.38, 95% CI [0.85, 2.26], P = 0.194).

Meta-regression

For the range of HbA1c cut-off values between 5.7% and 7.0%, there were no statistically significant effects on the development of major postoperative complications, overall postoperative complications, anastomotic leaks, overall infections, or wound infections (all P > 0.05). Bubble plots of the meta-regressions are presented in Supplementary Digital Content 11.

Discussion

Results from our meta-analysis showed that elevated HbA1c (> 6–7%) was associated with a higher risk of anastomotic leaks, wound infections, major postoperative complications (CD grades 3–5) and overall postoperative complications (CD grades 1–5), but not with overall infections and pneumonia.

The most important finding from this meta-analysis was that elevated HbA1c levels are associated with a higher risk of anasto-
motic leaks. This is an important observation as anastomotic leaks are one of the most serious complications associated with gastrointestinal surgery, resulting in a mortality rate as high as 16.4% and long hospital and intensive care unit admissions [36]. Another important finding was that wound infections were the only type of infection associated with elevated HbA1c levels. Taken together, these results indicate that elevated HbA1c levels may be an indicator of impairment in wound healing physiology. Impaired glucose tolerance causes both macrovascular and microvascular complications, which may result in inadequate angiogenesis and decreased perfusion to the wound site [37] as well as poorer immune function [38]. These results are consistent with previous findings regarding different types of surgeries with various levels of evidence [3,39,40]. If a target HbA1c level was set preoperatively for patients undergoing elective surgery, the risk of anastomotic leaks and wound infections could be markedly reduced.

Our meta-analysis also found that lower HbA1c levels are not only associated with a lower risk of major postoperative complications (CD grade 3–5), but also with a lower risk of overall postoperative complications (CD grade 1–5). This has significant implications as it suggests that postponing elective surgery until an optimal HbA1c level is achieved may reduce the risk of both major and overall postoperative complications that negatively affect patients’ quality of life after surgery. These findings may also facilitate counseling during preoperative assessments to motivate patients to make lifestyle modifications and improve medication adherence.

It should be noted that a significant association between preoperative HbA1c levels and the risk of overall infections and pneumonia was not found in our pooled results. These findings were not consistent with a well-cited study by Dronge et al. [41], who showed that a HbA1c cut-off value of 7% was significantly associated with lower postoperative infection risks in the major non-cardiac surgical population (which also included non-abdominal surgeries). This inconsistency could be explained by the different HbA1c cut-off values used, as Dronge et al. used a cut-off of 7%, while our study accepted a range between 6% and 7%. This may suggest that an HbA1c level of 6% may be too low for making prognoses regarding postoperative infections.

Regarding the rationales for excluding certain populations, patients undergoing pancreatic and bariatric surgery were excluded from this meta-analysis because the postoperative glucose metabolism in these patients is different from that in patients undergoing other types of abdominal surgeries [42,43]. As perioperative glucose control has been demonstrated to be an independent predictor of postoperative complications [44], we determined it would be unfair to group pancreatic and bariatric surgery patients with other non-pancreatic and non-bariatric patients undergoing surgery. Patients undergoing emergency surgery were also excluded because this patient population is different from that undergoing elective surgery, as these patients are by default subject to higher postoperative complications due to the nature of the surgery (e.g., unprepared bowel, fecal contamination, hemodynamic instability, sepsis). Additionally, preoperative HbA1c optimization is impossible in patients undergoing emergency surgery due to the lack of a preoperative period. Finally, transplant patients were excluded because the nature of transplant surgery is unique to that of major abdominal surgery, as defined in our Methods sections.

The main strength of this study is that this is the first meta-analysis investigating the association between preoperative HbA1c levels and postoperative complications exclusively in the elective major abdominal surgery population, as the majority of previous meta-analyses have been conducted on cardiac, bariatric, and orthopedic populations [3–5]. Another strength is our inclusion of the Chinese database CNKI, which helped to ensure an extensive search of the available literature, as the database has grown significantly in the past decade. Furthermore, the inclusion of the CNKI also ensures ethnic diversity and representation.

This meta-analysis has some limitations. Some studies that met the inclusion criteria of abdominal surgery had to be excluded since they also included non-abdominal surgeries, and we were unable to attain the data on abdominal surgeries separately. To overcome this limitation, we applied the Duval and Tweedie non-parametric trim and fill method to adjust the meta-analysis by incorporating theoretical missing trials. Some studies categorized patients according to their diabetes diagnosis status instead of their HbA1c status, and not everyone who had a diabetes diagnosis had an elevated HbA1c level. To adjust for this, we only included patients with HbA1c levels available and categorized them according to their HbA1c status. Another limitation was the inclusion of studies that used different HbA1c cut-off points. For this reason, we have provided a conservative conclusion that an HbA1c level > 6–7% is associated with higher risk of postoperative complications. Additionally, it was not possible to perform subgroup analyses, although these are crucial, accounting for the fact that some of the included patients had comorbidities such as cancer and patient-level data for these factors were unavailable. While this is a possible limitation, for diabetes optimization, HbA1c levels also allow for an attempt to optimize the preoperative phase similar to how we optimize pre-operative patients at high risk of malnutrition (for example, patients with gastrointestinal cancers).
The main implication of this study is to guide future RCTs. Our findings suggest that an elevated HbA1c level of 6–7% may be associated with a higher risk of postoperative complications. Currently, only the US guidelines recommend a target HbA1c of 7% [7], while the Great Britain and Australian guidelines recommend a target HbA1c of 8.5% and 9%, respectively [6,8]. Our findings may suggest that under the current guidelines, patients are undergoing elective surgery pre-optimized and would thus not have the best chance of being complication-free postoperatively. These implications should be considered with caution, however, as an association should not be mistaken for causation. Conducting an RCT to determine causation in the relationship between HbA1c levels and postoperative complications is necessary to determine if changes to the current guidelines are warranted. However, we accept that there are challenges in conducting RCTs in this field. Many elective major abdominal surgery operations are undertaken for cancer resection and are therefore urgent cases that do not allow sufficient time for the pre-optimization of HbA1c levels. Future studies should also investigate the specific HbA1c cut-off value that is associated with an increase in complications for different types of surgeries using a receiver-operating characteristic (ROC) analysis design.

In conclusion, the findings from our meta-analysis show that elevated HbA1c levels are associated with a higher risk of developing anastomotic leaks, wound infections, and major and overall postoperative complications, but not overall infections and pneumonia. This implies that patients fare better postoperatively if a target HbA1c level ≤ 7% is set before undergoing elective major abdominal surgery. Our findings can help to guide future RCTs to determine if current guidelines on the recommended cut-off values for HbA1c levels should be reviewed, as the HbA1c thresholds currently used in clinical practice are all above 7%. Further studies using ROC analyses to investigate the exact HbA1c cut-off value associated with an increase in postoperative complications should also be performed.

Funding

This work was supported by the funding department of the Department of Anesthesiology, Singapore General Hospital, Singapore. H.R.A. is a recipient of the SingHealth Duke-NUS Nurturing Clinician Scientists Scheme Award (project number 12/FY2017/P1/15-A29) and the National Medical Research Council (NMRC), Singapore, Clinician Investigator Salary Support scheme 2018–2020. The funding sources played no role in the design of this study or the analysis and interpretation of the results.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Joanna K. L. Wong (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft)
Yuhe Ke (Data curation; Formal analysis; Investigation; Methodology; Writing – original draft)
Yi Jing Ong (Data curation; Formal analysis; Investigation; Methodology; Writing – original draft)
HuiHua Li (Formal analysis; Investigation; Methodology; Writing – original draft)
Ting Hway Wong (Investigation; Methodology; Writing – review & editing)
Hairil Rizal Abdullah (Conceptualization; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Digital Content 1. Search strategy.
Supplementary Digital Content 2. Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards.
Supplementary Digital Content 3. Newcastle-Ottawa Scale for Risk of Bias Assessment of Studies
Supplementary Digital Content 4. Funnel plot of major postoperative complications.
Supplementary Digital Content 5. Funnel plot of overall complications (CD1 and above, using Wang et al’s data on postoperative infections).
Supplementary Digital Content 6. (A) Funnel plot and (B) forest plot of overall complications (CD1 and above, using Wang et al’s data on anastomotic leak) (P < 0.001).
Supplementary Digital Content 7. Funnel plot of all anastomotic leaks.
Supplementary Digital Content 8. Funnel plot of all infectious complications.
Supplementary Digital Content 9. Funnel plot of all wound infections.
Supplementary Digital Content 10. (A) Funnel plot and (B) forest plot of all pneumonia (P = 0.026).
Supplementary Digital Content 11. Bubble plots displaying meta-regression for (A) Major postoperative complications (CD3-5), (B) Overall postoperative complications (CD1-5), (C) Anasto-
motic leaks, (D) Overall infections, and (E) Wound infections.

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Effect of postoperative non-steroidal anti-inflammatory drugs on anastomotic leakage after pancreaticoduodenectomy

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Background: Although the association between an increase in anastomotic leakage (AL) and non-steroidal anti-inflammatory drugs (NSAIDs) has been reported in gastrointestinal surgeries, this issue has rarely been addressed for pancreaticoduodenectomy (PD). We aimed to investigate the association between postoperative NSAIDs administration and clinically relevant AL (CR-AL) following PD.

Methods: We retrospectively evaluated 2,163 consecutive patients who underwent PD between 2007 and 2019. The patients were divided into two groups; patients who received and did not receive NSAIDs by postoperative day (POD) 5. We conducted a propensity score analysis using inverse probability of treatment weighting (IPTW) to adjust the baseline differences between both groups. We compared the occurrence of CR-AL and other postoperative outcomes before and after IPTW. Further, we used the multivariable binary logistic regression method for a sensitivity analysis for CR-AL.

Results: A total of 2,136 patients were included in the analysis. Of these, 222 (10.4\%) received NSAIDs by POD 5. The overall occurrence rate of CR-AL was 14.9\%. After IPTW, postoperative NSAIDs were significantly associated with CR-AL (odds ratio [OR]: 1.24, 95\% CI [1.05, 1.47], \(P = 0.012\)), prolonged postoperative hospitalization (OR: 1.31, 95\% CI [1.14, 1.50], \(P < 0.001\)), and unplanned readmission within 30 days postoperatively (OR 1.48: 95\% CI [1.15, 1.91], \(P = 0.002\)). However, this association was not consistent in the sensitivity analysis.

Conclusions: Postoperative NSAIDs use was significantly associated with an increase in CR-AL incidence following PD. However, sensitivity analysis failed to show its association, which precludes a firm conclusion of its detrimental effect.

Keywords: Analgesics; Anastomotic leak; Non-steroidal anti-inflammatory agents; Pancreatic fistula; Pancreaticoduodenectomy; Postoperative complications.
tactors to postoperative morbidity, prolonged hospitalization, and mortality after PD [1,2]. Thus, several efforts have been made to identify their risk factors [3–5].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used non-opioid analgesics in multimodal analgesia, which improve postoperative analgesia while reducing opioid-related side effects due to their opioid-sparing effect [6]. However, several studies have reported the possible harmful association of NSAIDs and ALs in gastrointestinal surgeries [7,8]. In several preclinical studies, NSAIDs have been reported to impair collagen deposition and angiogenesis in healing tissues, which may decrease the strength of the anastomosis and lead to an AL [9,10].

However, the detrimental effect of NSAIDs on AL following a PD has rarely been reported [11–13]. Therefore, investigating the association between NSAID use and the risk of AL, including postoperative pancreatic fistula (POPF), which is the most challenging complication following a PD, is important. In this retrospective study, we conducted a propensity score analysis with inverse probability of treatment weighting (IPTW) to investigate the association between early postoperative NSAID use and the occurrence of clinically relevant AL (CR-AL) in patients with PD.

Materials and Methods

This retrospective observational study was approved by the Institutional Review Board of Seoul National University Hospital (No. 2010-145-1167). The need for informed patient consent was waived due to the anonymization of their medical records before analysis. The manuscript is prepared following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [14].

We retroactively reviewed the electronic medical records of 2,163 consecutive adult patients who underwent classic PD (Whipple’s operation) or pylorus-preserving PD (PPPD) for various peripancreatic lesions at our institution from January 2007 to December 2019. We did not perform a priori or post-hoc power calculation due to the retrospective design of the study, and all patients who met the abovementioned inclusion criteria were included in the analysis. Patients with missing values for the covariates used in the propensity score calculation (total, n = 10; pancreatic texture, n = 6; and pancreatic duct size, n = 4), patients who died within 30 days after surgery (n = 11), and patients who underwent total pancreatectomy (n = 2) or hepatoduodenectomy (n = 1) due to remnant pancreatic cancer after PD or PPPD during hospitalization were excluded. Patients who received laparoscopic PD were also excluded due to their small number (n = 3). A total of 2,136 patients were included in the final analysis.

The cohort was divided into two groups: patients who received NSAIDs (NSAID group) and those who did not receive NSAIDs (no NSAID group) by postoperative day (POD) 5. In our institution, during the study period, the main postoperative analgesic method was intravenous patient-controlled analgesia (IV-PCA).

By March 2019, IV-PCA comprised a mixture of fentanyl and morphine in a bolus of 1 ml (intravenous morphine equivalent dose [IVMED] 1–2.5 mg) with a lockout interval of 15 min and a basal infusion rate of 1 ml/h (IVMED 1–2.5 mg/h). Since April 2019, we have used the IV-PCA comprising only fentanyl, and in July 2019, we introduced the IV-PCA without basal infusion [15]. Ketorolac has been administered as an intravenous rescue analgesic based on the attending surgeon’s preference, and ibuprofen has also been administered as an oral rescue analgesic after the resumption of oral intake. Additionally, we investigated all types of NSAIDs available in our institution, including cyclooxygenase (COX)-2 inhibitors. Apart from NSAIDs, morphine, fentanyl, tramadol, and acetaminophen were also administered as intravenous rescue analgesics based on the attending surgeon’s preference. In our institution, epidural PCA has been used since 2019 in patients scheduled to receive open PD and agreed to it without contraindications of neuraxial anesthesia. Epidural PCA comprised 0.15% ropivacaine with 2 μg/ml fentanyl at a basal infusion rate of 4 ml/h and a bolus of 2 ml with a lockout interval of 20 min.

Data on sex, age, body mass index (BMI), smoking, American Society of Anesthesiologists (ASA) physical status classification, pathologic diagnosis, surgical procedure (classic PD vs. PPPD), type of surgical approach (open vs. robot-assisted), neoadjuvant chemotherapy and radiotherapy, preoperative biliary drainage (percutaneous transhepatic biliary drainage or endoscopic retrograde biliary drainage), pathological type, pancreatic duct diameter (mm), pancreatic texture (soft vs. firm), type of pancreatic duct stent (internal, external), estimated blood loss (EBL, ml), intraoperative crystalloid and colloid administration (ml), intraoperative vasopressor use, intraoperative packed red blood cell transfusion, operative time (min), postoperative length of hospital stay (LOS), and reoperation or unplanned readmission within 30 days postoperatively were collected retrospectively using the Seoul National University Hospital Patients Research Environment system. Vasopressors included ephedrine, phentylephrine, norepinephrine, dopamine, or epinephrine. We also extracted information on postoperative complications, including on ALs, from the surgeon’s database.

In our institution, PPPD is the standard procedure for peripancreatic lesions. However, if there is a lesion such as duodenal ulcer, ischemia, and tumor infiltration, PD is also performed at the surgeon’s discretion. The robot-assisted approach has been used.
since 2015, and the scope of surgery or the anastomosis method is the same as that for open surgery. PJ anastomosis is performed in a two-layer, end-to-side, duct-to-mucosal manner with an internal or external stent [16]. Jackson–Pratt drains are routinely placed adjacent to the PJ site, and an early drain removal strategy (POD 3–5) is favored. To detect any postoperative complications, amylase concentrations in serum and drainage fluid are measured postoperatively (on POD 1, 3, 5, 7, and 10) in all patients, and contrast-enhanced computed tomography scans are performed on POD 5–7. Peripancreatic drains are removed in case of no evidence of leakage.

The primary outcome of the study was the occurrence of CR-ALs. CR-AL was defined as clinically relevant postoperative pancreatic fistula (CR-POPF) or CR-HJ anastomotic leakage (CR-HL). CR-POPF was defined according to the International Study Group on Pancreatic Fistula criteria grades B and C [17]. CR-HL was defined based on the proposed grading system for HJ leakage grade B and C [5]. The secondary outcomes included postoperative acute kidney injury, wound complication, postoperative bleeding, delayed gastric emptying, prolonged postoperative hospitalization, re-operation, and unplanned re-admission within 30 days postoperatively. Postoperative bleeding was defined as the need for postoperative transfusion or operation, embolization, or endoscopic hemostasis for bleeding control. Wound complication was defined as the case when aggressive wound dressing, wound repair, or late wound drain removal was required. Delayed gastric emptying was defined as the need to retain nasogastric drainage for 10 days after surgery or the inability to tolerate a semisolid diet 14 days after surgery. Prolonged postoperative hospitalization was defined as a LOS > 75th percentile of that observed for our cohort (> 19 days).

**Statistical analysis**

R version 3.6.3 (R Foundation for Statistical Computing, Austria) was used for the statistical analysis. Statistical significance was set as a two-sided P < 0.05. The normality of data distribution was assessed using a Shapiro–Wilk test. Categorical data were expressed as number (%) and continuous data as median (Q1, Q3). We did not replace missing values for the variables of baseline characteristics.

To evaluate the association between postoperative NSAID use and primary and secondary outcomes, we performed an IPTW analysis using a propensity score [18]. Patients with a probability value of 0 or 1 for receiving postoperative NSAID were excluded from the analyses based on the positivity assumption. In addition, extreme weights greater than the 99th percentile or less than the lowest first percentile were replaced with the value of the 99th percentile or the first percentile, respectively [18]. Balance in variables between the two groups before and after IPTW was evaluated by calculating the standardized mean difference (SMD). The following variables were used as contributors to the propensity score: sex, age, BMI, ASA physical status, neoadjuvant chemotherapy, type of surgical approach, pancreatic texture, pancreatic duct diameter, type of pancreatic duct stent, pathological type (pancreatic adenocarcinoma or pancreatitis vs. all others), EBL (≤ 400 ml, 401–700 ml, 701–1,000 ml, and > 1,000 ml), and intraoperative crystalloid amount per 100 ml. Then, we calculated the odds ratio (OR) and 95% CI of postoperative NSAID use on the primary and secondary outcomes before and after IPTW.

For a sensitivity analysis, we performed multivariable binary logistic regression analyses for CR-AL and CR-POPF. Based on previous studies regarding the risk factors of POPF [4,16,19,20], the following variables were included in the analyses: postoperative NSAID use within POD 5, sex, age, BMI, ASA physical status III or IV (vs. I or II), smoking, neoadjuvant radiation therapy, neoadjuvant chemotherapy, pathological type (pancreatic adenocarcinoma or pancreatitis vs. all others), robotic-assisted surgery (vs. open), type of pancreatic duct stent (external vs. none vs. internal), soft pancreatic gland (vs. firm), pancreatic duct diameter (mm), operative time (min), EBL (≤ 400 ml, 401–700 ml, 701–1,000 ml, > 1,000 ml), intraoperative vasopressor use, intraoperative transfusion, and crystalloid and colloid administration per 100 ml. We did not perform preliminary variable selection by univariable logistic regression analysis before multivariable analysis. We investigated 10 interactions between the following five variables using a likelihood ratio test: crystalloid administration per 100 ml, colloid administration per 100 ml, intraoperative vasopressor use, intraoperative transfusion, and EBL. Statistically significant interaction terms were included in our final multivariable analysis. The linearity assumption between each continuous variable and the binary outcome variable was examined using restricted cubic splines.

Finally, we classified patients into four groups according to the 10-point fistula risk score (0: negligible, 1–2: low, 3–6: intermediate, 7–10: high) [21], and conducted the aforementioned analyses in the subgroup with intermediate to high risk of CR-POPF.

**Results**

Among the 2,136 patients included in the analysis, 222 (10.4%) received NSAIDs within POD 5. Among them, 204 (9.6%) received ketorolac with a median (Q1, Q3) value of 30 (30, 60) mg, and 21 (1.0%) received oral ibuprofen with a median (Q1, Q3)
value of 800 (600, 1650) mg. No other intravenous NSAIDs were administered during that period. During the study period, the overall incidence rates of CR-POPF, CR-HL, and CR-AL were 14.1%, 1.3%, and 14.9%, respectively. There was no GJ anastomosis leakage in the total cohort. Fig. 1 presents the annual occurrence of CR-AL and the major treatment changes in PD in our institution.

Comparisons of demographic and clinical characteristics between the two groups before and after IPTW are shown in Table 1 and Supplementary Table 1. Before IPTW, age, pathology, preoperative albumin, neoadjuvant chemotherapy, type of pancreatic stent, pancreatic duct size, fistula risk score, and intraoperative crystalloid amount were significantly different between the two groups (SMD > 0.1), but there were no significant differences in those variables except pathology and neoadjuvant radiation therapy between the two groups after IPTW (Table 1, Supplementary Table 1). Supplementary Table 2 compares the demographics and clinical characteristics between the two groups before and after IPTW in the subgroup with intermediate to high risk of CR-POPF.

Table 2 compares the primary and secondary outcomes of our study after IPTW. Postoperative NSAID use was significantly associated with CR-AL after IPTW (OR: 1.24, 95% CI [1.05, 1.47], P = 0.012). Furthermore, the incidence of postoperative bleeding (OR: 1.57, 95% CI [1.08, 2.30], P = 0.018), delayed gastric emptying (OR: 1.35, 95% CI [1.04, 1.74], P = 0.024), proportions of prolonged postoperative hospitalization (OR: 1.31, 95% CI [1.14, 1.50], P < 0.001), and unplanned readmission within 30 days postoperatively (OR: 1.48, 95% CI [1.15, 1.91], P = 0.002) were significantly higher in the NSAID group than in the no NSAID group after IPTW. In the subgroup analysis, postoperative NSAID use was also significantly associated with CR-AL after IPTW (OR: 1.30, 95% CI [1.09, 1.54], P = 0.004), delayed gastric emptying (OR: 1.69, 95% CI [1.28, 2.24], P < 0.001), prolonged postoperative hospitalization (OR: 1.41, 95% CI [1.22, 1.64], P < 0.001), and unplanned readmission within 30 days postoperatively (OR: 1.48, 95% CI [1.13, 1.93], P = 0.005; Supplementary Table 3).

In multivariable logistic regression analysis, female sex, higher BMI, neoadjuvant chemotherapy, pancreatic adenocarcinoma or pancreatitis, soft pancreatic texture, smaller pancreatic duct size, and internal pancreatic stent were identified as significant predictors of both CR-AL and CR-POPF (Table 3). Additionally, older age was identified as a significant predictor of CR-AL. However, postoperative NSAID use was not significantly associated with CR-AL (OR: 1.19, 95% CI [0.81, 1.76], P = 0.376) and CR-POPF.

Fig. 1. Annual surgical volume, occurrence of CR-AL, and perioperative parameters according to the year of surgery. Bars indicate number of patients and lines indicate proportion (%). CR-AL: clinically relevant anastomotic leakage, NSAIDs: non-steroidal anti-inflammatory drugs.
### Table 1. Demographic and Clinical Characteristics between Patients with and without Postoperative NSAIDs Use

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Before IPTW</th>
<th>After IPTW</th>
<th>SMD</th>
<th>Before IPTW</th>
<th>After IPTW</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65 (58, 72)</td>
<td>63 (57, 70)</td>
<td>0.159</td>
<td>65 (58, 71)</td>
<td>64 (57, 70)</td>
<td>0.011</td>
</tr>
<tr>
<td>F (vs. M)</td>
<td>751 (39.2)</td>
<td>89 (40.1)</td>
<td>0.017</td>
<td>841 (39.4)</td>
<td>757 (40.4)</td>
<td>0.020</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 (21.2, 25.2)</td>
<td>23.6 (21.5, 25.5)</td>
<td>0.084</td>
<td>23.2 (21.2, 25.2)</td>
<td>23.4 (21.3, 25.3)</td>
<td>0.016</td>
</tr>
<tr>
<td>Background medical status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA-PS (I/II/III/IV)</td>
<td>371 (19.4)/1,385 (72.4)/157 (8.2)/1 (0.1)</td>
<td>40 (18.0)/164 (73.9)/18 (8.1)/0</td>
<td>0.049</td>
<td>412 (19.3)/1,548 (72.5)/175 (8.2)/1 (0)</td>
<td>337 (18.0)/1,363 (72.7)/175 (9.3)/0</td>
<td>0.057</td>
</tr>
<tr>
<td>Preoperative albumin (g/dl)</td>
<td>3.9 (3.6, 4.2)</td>
<td>4.0 (3.7, 4.3)</td>
<td>0.167</td>
<td>3.9 (3.6, 4.2)</td>
<td>4.0 (3.6, 4.2)</td>
<td>0.081</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma or pancreatitis (vs. all others)</td>
<td>582 (30.4)</td>
<td>65 (29.3)</td>
<td>0.025</td>
<td>647 (30.3)</td>
<td>543 (28.9)</td>
<td>0.029</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>148 (7.7)</td>
<td>9 (4.1)</td>
<td>0.157</td>
<td>157 (7.4)</td>
<td>105 (5.6)</td>
<td>0.071</td>
</tr>
<tr>
<td>Operation and anesthesia related</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPPD (vs. Whipple’s operation)</td>
<td>1,449 (75.7)</td>
<td>167 (75.2)</td>
<td>0.111</td>
<td>1,622 (75.9)</td>
<td>1,416 (75.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Robot-assisted (vs. open)</td>
<td>182 (9.5)</td>
<td>27 (12.2)</td>
<td>0.085</td>
<td>209 (9.8)</td>
<td>182 (9.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pancreatic stent (None/external/internal)</td>
<td>91 (4.8)/782 (40.9)/1,041 (54.4)</td>
<td>14 (6.3)/104 (46.8)/104 (46.8)</td>
<td>0.155</td>
<td>105 (4.9)/886 (41.5)/1,145 (53.6)</td>
<td>98 (5.2)/833 (44.4)/943 (50.3)</td>
<td>0.066</td>
</tr>
<tr>
<td>Soft pancreas (vs. firm)</td>
<td>1,280 (66.9)</td>
<td>156 (70.3)</td>
<td>0.087</td>
<td>1,437 (67.2)</td>
<td>1,295 (69.1)</td>
<td>0.040</td>
</tr>
<tr>
<td>Pancreatic duct size (mm)</td>
<td>3 (2, 4)</td>
<td>3 (2, 4)</td>
<td>0.156</td>
<td>3 (2, 4)</td>
<td>3 (2, 4)</td>
<td>0.012</td>
</tr>
<tr>
<td>EBL (ml)</td>
<td>400 (250, 600)</td>
<td>350 (200, 550)</td>
<td>0.048</td>
<td>400 (250, 600)</td>
<td>374 (200, 550)</td>
<td>0.027</td>
</tr>
<tr>
<td>Fistula risk score</td>
<td>5 (3, 6)</td>
<td>5 (3, 6)</td>
<td>0.131</td>
<td>5 (3, 6)</td>
<td>5 (3, 6)</td>
<td>0.012</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>312 (258, 370)</td>
<td>315 (270, 375)</td>
<td>0.073</td>
<td>315 (260, 372)</td>
<td>310 (268, 367)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or number (%). NSAID: non-steroidal anti-inflammatory drugs, IPTW: inverse probability of treatment weighting, BMI: body mass index, ASA-PS: American Society of Anesthesiologists physical status, PPPD: pylorus-preserving pancreaticoduodenectomy, SMD: standardized difference, EBL: estimated blood loss.

### Table 2. Comparison of the Primary and Secondary Outcomes between PD Patients with and without Postoperative NSAIDs Use after IPTW

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>No NSAID group (n = 2,136)</th>
<th>NSAID group (n = 1,875)</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR-AL</td>
<td>313 (14.7)</td>
<td>332 (17.7)</td>
<td>0.012</td>
<td>1.24 (1.05, 1.47)</td>
</tr>
<tr>
<td>CR-POPF</td>
<td>300 (14.0)</td>
<td>291 (15.5)</td>
<td>0.184</td>
<td>1.13 (0.95, 1.34)</td>
</tr>
<tr>
<td>CR-HL</td>
<td>20 (0.9)</td>
<td>54 (2.9)</td>
<td>&lt; 0.001</td>
<td>3.11 (1.86, 5.21)</td>
</tr>
<tr>
<td>Any POPF</td>
<td>1,237 (57.9)</td>
<td>1,116 (59.5)</td>
<td>0.300</td>
<td>1.07 (0.94, 1.21)</td>
</tr>
<tr>
<td>Any HL</td>
<td>23 (1.1)</td>
<td>54 (2.9)</td>
<td>&lt; 0.001</td>
<td>2.67 (1.63, 4.35)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>4.6 (0.2)</td>
<td>9.2 (0.5)</td>
<td>0.145</td>
<td>2.30 (0.75, 7.09)</td>
</tr>
<tr>
<td>Wound problem</td>
<td>197 (9.2)</td>
<td>183 (9.8)</td>
<td>0.557</td>
<td>1.07 (0.86, 1.32)</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>48 (2.3)</td>
<td>66 (3.5)</td>
<td>0.018</td>
<td>1.57 (1.08, 2.30)</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>116 (5.4)</td>
<td>135 (7.2)</td>
<td>0.024</td>
<td>1.35 (1.04, 1.74)</td>
</tr>
<tr>
<td>Prolonged postoperative hospitalization</td>
<td>522 (24.4)</td>
<td>557 (29.7)</td>
<td>&lt; 0.001</td>
<td>1.31 (1.14, 1.50)</td>
</tr>
<tr>
<td>Reoperation within 30 days after surgery</td>
<td>17 (0.8)</td>
<td>19 (1.0)</td>
<td>0.451</td>
<td>1.29 (0.67, 2.49)</td>
</tr>
<tr>
<td>Unplanned readmission within 30 days after surgery</td>
<td>115 (5.4)</td>
<td>146 (7.8)</td>
<td>0.002</td>
<td>1.48 (1.15, 1.91)</td>
</tr>
</tbody>
</table>


(OR: 1.07, 95% CI [0.71, 1.60], P = 0.754; Table 3). Supplementary Table 4 shows the results of the multivariable logistic regression analysis for CR-POPF in the subgroup with intermediate to high risk of CR-POPF. In the subgroup analysis, significant associations of all the aforementioned factors except age were maintained.

https://doi.org/10.4097/kja.21096
In this study, we investigated the association between postoperative NSAID use and CR-AL in patients who underwent PD. Our results with rigorous multivariable adjustments showed a significant association between postoperative NSAID use and CR-AL, especially CR-HL. Additionally, postoperative NSAIDs were significantly associated with prolonged postoperative hospitalization and unplanned readmission within 30 days postoperatively after IPTW.

NSAIDs should be used cautiously due to their possible detrimental effect on anastomotic healing. A recent systematic review and meta-analysis provided evidence of this detrimental effect on gastrointestinal anastomoses, although most of the studies included were conducted in patients with colorectal surgery [22]. Further, in a large cohort study using the nationwide claim database, perioperative ketorolac use was associated with an increase in emergency department visits, re-intervention rate, and readmission rate within 30 days postoperatively not only in colorectal but also in non-colorectal gastrointestinal surgeries [8]. In addition, impairment of angiogenesis and collagen deposition are possible mechanisms of NSAID-induced AL that can contribute to AL following a PD [12,13,23,24]. Therefore, it is important to deliberate on the possible detrimental effects of NSAIDs before prescribing them as an option for multimodal analgesia for patients undergoing PD.

Previous retrospective studies have reported negative results regarding the association between postoperative NSAID use and CR-POPF after PD. The first report related to this issue failed to show an association between postoperative non-selective NSAIDs use and POPF [12]. However, the study had critical shortcomings: not adjusting for important confounders, such as pancreatic tex-

### Table 3. Binary Logistic Regression Analysis for Factors Associated with CR-AL or CR-POPF

<table>
<thead>
<tr>
<th>Variable</th>
<th>CR-POPF OR (95% CI)</th>
<th>P value</th>
<th>CR-AL OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative NSAIDs use</td>
<td>1.07 (0.71, 1.60)</td>
<td>0.754</td>
<td>1.19 (0.81, 1.76)</td>
<td>0.376</td>
</tr>
<tr>
<td>F (vs. M)</td>
<td>0.49 (0.37, 0.66)</td>
<td>&lt; 0.001</td>
<td>0.55 (0.41, 0.73)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.127</td>
<td>1.01 (1.00, 1.03)</td>
<td>0.038</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.09 (1.04, 1.13)</td>
<td>&lt; 0.001</td>
<td>1.08 (1.04, 1.13)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.84 (0.58, 1.22)</td>
<td>0.363</td>
<td>0.87 (0.60, 1.25)</td>
<td>0.449</td>
</tr>
<tr>
<td>ASA-PS III (vs. I or II)</td>
<td>0.80 (0.47, 1.35)</td>
<td>0.398</td>
<td>0.82 (0.49, 1.37)</td>
<td>0.450</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>0.20 (0.05, 0.79)</td>
<td>0.022</td>
<td>0.18 (0.05, 0.72)</td>
<td>0.015</td>
</tr>
<tr>
<td>Neoadjuvant radiation therapy</td>
<td>0.84 (0.08, 9.23)</td>
<td>0.889</td>
<td>1.58 (0.23, 10.89)</td>
<td>0.645</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma or pancreatitis (vs. all others)</td>
<td>0.37 (0.25, 0.56)</td>
<td>&lt; 0.001</td>
<td>0.45 (0.31, 0.65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Robotic-assisted surgery (vs. open)</td>
<td>0.79 (0.48, 1.31)</td>
<td>0.367</td>
<td>0.84 (0.53, 1.35)</td>
<td>0.471</td>
</tr>
</tbody>
</table>


### Discussion

In this study, we investigated the association between postoperative NSAID use and CR-AL in patients who underwent PD. Our results with rigorous multivariable adjustments showed a significant association between postoperative NSAID use and CR-AL, especially CR-HL. Additionally, postoperative NSAIDs were significantly associated with prolonged postoperative hospitalization and unplanned readmission within 30 days postoperatively after IPTW.

NSAIDs should be used cautiously due to their possible detrimental effect on anastomotic healing. A recent systematic review and meta-analysis provided evidence of this detrimental effect on gastrointestinal anastomoses, although most of the studies included were conducted in patients with colorectal surgery [22]. Further, in a large cohort study using the nationwide claim database, perioperative ketorolac use was associated with an increase in emergency department visits, re-intervention rate, and readmission rate within 30 days postoperatively not only in colorectal but also in non-colorectal gastrointestinal surgeries [8]. In addition, impairment of angiogenesis and collagen deposition are possible mechanisms of NSAID-induced AL that can contribute to AL following a PD [12,13,23,24]. Therefore, it is important to deliberate on the possible detrimental effects of NSAIDs before prescribing them as an option for multimodal analgesia for patients undergoing PD.

Previous retrospective studies have reported negative results regarding the association between postoperative NSAID use and CR-POPF after PD. The first report related to this issue failed to show an association between postoperative non-selective NSAIDs use and POPF [12]. However, the study had critical shortcomings: not adjusting for important confounders, such as pancreatic tex-
ture and pancreatic duct size, and a small sample size. Since then, a subsequent study reported that early postoperative ketorolac use was associated with an increase in the incidence of any POPF, including biological leakage [13]. However, there was no significant association between postoperative ketorolac use and CR-POPF. In addition, the study had a small sample size, and there was no information about pancreatic gland texture and duct size in approximately 30% of the patients. The most recent study reported no association between postoperative ketorolac use and CR-POPF [11]. However, it was still difficult to conclude the safety of using ketorolac for PD due to their wide CI, including substantial adverse effects (any ketorolac, OR: 1.99, 95% CI [0.93, 4.26], P = 0.08), but the authors supported the safety of using ketorolac for PD, noting that the incidence of CR-POPF remained stable despite the great increase in the use of ketorolac at their institution. However, the improvement in surgical treatment and accumulated surgeon's experience could have offset the harmful effect of ketorolac on ALs [3].

Compared to previous studies, our study differed in the following respects. First, we performed adjustment analyses with a higher number of confounders reported to be associated with the occurrence of CR-AL. Among them, intraoperative fluid administration was a newly identified predictor of CR-AL in this study. Perioperative fluid administration was reported as a risk factor for AL after colorectal surgery [25]. From the perspective of an anesthesiologist, further research is required on the effect of other intraoperative variables on the development of CR-AL [26]. Second, we included both HL and PJ ALs in the primary outcome. We assumed that NSAID could affect all types of gastrointestinal anastomosis. Third, we increased the statistical power of our findings using the IPTW analysis [18]. Through this method, we tried to overcome the disadvantage of relatively fewer patients in the NSAID group and could perform subgroup analyses for the risk of CR-POPF. Considering that the incidence rate of CR-AL is 15% and an OR of 1.3 is clinically important, at least 1,636 patients are required for each group to achieve 80% power to detect a difference between the two groups with a two-sided α of 0.05. Therefore, to identify the detrimental effect of NSAIDs on AL in PD, a large-scale study is required, as those conducted for colorectal surgery [7, 8].

In our study, postoperative NSAID use showed a significant association with an increase in postoperative bleeding, delayed gastric emptying, prolonged postoperative hospitalization, and unplanned readmission, as well as an increase in CR-AL occurrence after IPTW. Since CR-AL might largely contribute to postoperative bleeding or delayed gastric emptying after PD [27, 28], postoperative NSAIDs use could increase these complications would have led to the prolonged hospitalization and readmission rate after PD.

As an expert in postoperative pain management, anesthesiologists should try to explore other effective analgesic methods, including regional analgesia, in patients undergoing PD and avoid the use of NSAIDs. With the advent of the opioid crisis, the use of opioids in major abdominal surgeries is being discouraged. Epidural analgesia, previously known as the gold standard for postoperative pain control after major abdominal surgeries, is also being replaced by another multimodal analgesia due to disadvantages such as hypotension, urinary retention, rare but serious complications, and low cost-effectiveness [29, 30]. Therefore, anesthesiologists should find the optimal analgesic method to effectively control postoperative pain while reducing postoperative complications in patients undergoing PD, based on the latest evidence.

However, our results should be interpreted cautiously for the following reasons. First, an inherent limitation of the retrospective nature of this study is that unmeasured and unknown confounders may have affected our results, although we performed IPTW to reduce the bias. Our results could not demonstrate a causal relationship but only reveal associations. Second, this study analyzed a cohort of a single tertiary hospital in Korea. Therefore, center-specific factors and the ethnic uniformity of the cohort limit the generalizability of our findings. Third, we could not consider the effect of surgeons’ experience, such as surgical skills, on the occurrence of POPF [3, 31]. However, our results were obtained from the leading institution in South Korea in this field, with a large hospital volume [32]. During the study period, the incidence rate of CR-AL in our institution was lower than in other institutions [3]. Therefore, the effect of surgeons’ experience on the primary outcome in this study would have been small. Fourth, the median value of the ketorolac dose in this study was 30 mg, which was relatively small compared to that in previous studies [11–13]. Therefore, we could not identify the dose-dependent effect of ketorolac on the development of POPF. Fifth, although our primary outcome included both PJ and HJ ALs, adjustment for confounders was mainly focused on the risk of PJ AL. HJ AL is relatively rare, and its risk factors are not well-known. Last, if there was a large imbalance in the treatment allocation as in our study, IPTW could affect the results by giving excessive weights to some marginal subjects. However, IPTW can operate without significant increase in the type I error rate in the context of low prevalence of treatment [33]. We also performed weight truncation to reduce excessive weights.

In conclusion, we found a significant association between the use of postoperative NSAIDs and the occurrence of CR-AL in pa-
patients with PD. This detrimental effect of postoperative NSAID use could lead to an increase in prolonged postoperative hospitalization and unplanned readmission within 30 days after surgery. However, the significant association only presented in CR-HL, and the rarity of CR-HL precludes a firm conclusion regarding the clinically meaningful detrimental effect of its use in these patients. Further sensitivity analysis failed to show its detrimental effect. Our study supports the demand for more research with sufficient power on the effects of NSAIDs on AL following a PD.

**Funding**

None.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Author Contributions**

Susie Yoon (Formal analysis; Writing – original draft)
Hyerin Kim (Data curation)
Hye-Yeon Cho (Data curation)
Ho-Jin Lee (Conceptualization; Formal analysis; Supervision; Writing – review & editing)
Hongbeom Kim (Data curation)
Hyung-Chul Lee (Data curation)
Jin-Young Jang (Data curation; Writing – review & editing)

**Supplementary Materials**

Supplementary Table 1. Baseline and perioperative variables between patients with and without postoperative non-steroidal anti-inflammatory drugs (NSAIDs) use before and after inverse probability of treatment weighting (IPTW) in the total cohort
Supplementary Table 2. Baseline and perioperative variables between patients with and without postoperative non-steroidal anti-inflammatory drugs (NSAIDs) use before and after inverse probability of treatment weighting (IPTW) in the subgroup with intermediate to high risk of CR-POPF
Supplementary Table 3. Comparison of the primary and secondary outcomes between patients with and without postoperative non-steroidal anti-inflammatory drugs (NSAIDs) use after pancreaticoduodenectomy before and after inverse probability of treatment weighting (IPTW) in the subgroup with intermediate to high risk of clinically relevant postoperative pancreatic fistula (CR-POPF)

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Effects of dexamethasone on catheter-related bladder discomfort and emergence agitation: a prospective, randomized, controlled trial

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Background: Catheter-related bladder discomfort (CRBD) is common in patients with a urinary catheter and is a risk factor for emergence agitation (EA). The mainstay of CRBD management is anticholinergics. Dexamethasone inhibits acetylcholine release. This study aimed to evaluate the effects of dexamethasone on postoperative CRBD and EA.

Methods: In this prospective study, 90 patients undergoing urological surgery requiring urinary catheterization were allocated randomly to one of two groups (each n = 45). Before induction of anesthesia, the dexamethasone group received 10 mg (2 ml) of dexamethasone intravenously, while the control group received 2 ml of saline in the same manner. The incidence and severity of CRBD were assessed 0, 1, 2, and 6 h after the patient arrived in the post-anesthesia care unit (PACU) as the primary outcomes. The incidence and severity of EA were also compared during emergence and recovery from anesthesia as secondary outcomes.

Results: The incidences of CRBD in the control group and dexamethasone group at 0, 1, 2, and 6 h postoperatively were 28.9% and 15.6%, 55.6% and 55.6%, 57.8% and 46.7%, and 53.3% and 51.1%, respectively. The incidence and severity of CRBD assessed at 0, 1, 2, and 6 h postoperatively did not show intergroup differences. The incidence and severity of EA in the operating room and PACU also showed no difference between the groups.

Conclusions: Dexamethasone (10 mg) administered before induction of anesthesia did not further reduce the incidence or severity of CRBD or EA in patients undergoing urological surgery.

Keywords: Anesthesia; Catheters; Catheterization; Dexamethasone; Incidence; Urinary bladder.

Introduction

Urinary catheterization is performed during urological surgery to empty and irrigate the bladder, prevent urethral injury, the formation of blood clots, reimplantation of cancer cells, and short-term voiding failure, and to allow monitoring of postoperative bleeding and urinary output. However, 47–90% of patients with a urinary catheter experience catheter-related bladder discomfort (CRBD), defined as an unpleasant and burning sensation in the urethra and suprapubic area [1]. CRBD causes significant postoperative distress, often accompanied by behavioral responses, such as loud complaining, flailing limbs, and attempts to remove the urinary catheter [2,3]. These responses can lead to in-
increased medical-staff workload, exacerbation of postoperative pain, poor quality of life, extended hospital stay, and an increased incidence of postoperative complications, including bleeding, surgical wound dehiscence, arrhythmias, and hemodynamic instability [2]. Therefore, prevention and early management of CRBD is clinically important, and many interventions have been proposed [1–4]. The mainstay of treatment for CRBD is anticholinergic agents that inhibit M3 and particularly M2, muscarinic receptors [1,2]. Inhibitors of prostaglandin (PG) synthesis, such as paracetamol, also reduce the severity of CRBD [3].

Meanwhile, the presence of a urinary catheter, as well as CRBD secondary to an indwelling urinary catheter, can increase the risk for emergence agitation (EA) [5,6]. EA may result in an increase in bleeding at the surgical site, injury to the self or medical staff, unintended extubation, accidental removal of catheters, and increased medical care costs [6].

The synthetic glucocorticoid dexamethasone inhibits acetylcholine release by increasing inhibitory M4 muscarinic receptor function [7], and represses PG synthesis by antagonizing upregulation of cyclooxygenase (COX) [8]. In addition, the anti-inflammatory, antiemetic, and analgesic effects of dexamethasone may reduce sore throat, postoperative nausea and vomiting (PONV), and pain, which are known risk factors for EA [6,9,10]. This study was designed to evaluate the effects of dexamethasone on CRBD and EA in patients undergoing elective urological surgery.

Materials and Methods

The Institutional Review Board of Konyang University Hospital approved this investigation (approval number: KYUH 2018-02-001-002) and the protocol was registered with the Korean Clinical Research Information Service. This prospective, randomized, placebo-controlled study was conducted from May 2018 through October 2018 in a single university hospital (Konyang University Hospital, Daejeon, Korea) after obtaining written informed consent from all participants. This clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. The study included 19 to 80-year-old patients with American Society of Anesthesiologists physical status I–III, who were scheduled for urological surgery requiring urinary catheterization. A patient was excluded if any of the following criteria were met: (1) immunosuppression; (2) active infection; (3) bladder outlet obstruction; (4) overactive bladder (OAB; urinary frequency > 3 times per night or > 8 times in 24 h); (5) prostate hypertrophy; (6) end-stage renal disease; (7) neuropsychological disorder or cognitive impairment; (8) uncontrolled diabetes; or (9) undergoing urological surgery with an anesthesia duration expected to exceed 6 h (considering the plasma half-life of dexamethasone of approximately 6 h) [11].

Patients were allocated randomly (1 : 1 allocation ratio) to one of two groups (control or dexamethasone group) using a random number table generated using online randomization software (www.randomizer.org). The allocations were concealed in opaque envelopes and opened when the patient arrived in the preanesthetic holding area by the anesthetic nurse responsible for preparing the study drugs (saline for the control group and dexamethasone for the dexamethasone group). The anesthetic nurse was blinded to the purpose of the study and was not involved in data collection. In addition, the patients, the anesthesiologist who evaluated the outcome variables, and the urologist who performed the urinary catheterization were blinded to group allocation.

All patients fasted for at least 8 h and entered the operating room without premedication. Routine monitoring included pulse oximetry, electrocardiography, noninvasive automated blood pressure monitoring, the Patient State Index (PSI) (SedLine®, Masimo Corp., USA), and neuromuscular train-of-four (TOF) acceleromyography (TOF-Watch SX®, Organon Ltd., Ireland) on the adductor pollicis muscle. Immediately before induction of anesthesia, patients in the dexamethasone group received 10 mg (2 ml; 5 mg/ml) of dexamethasone sodium phosphate (Yuhan Co., Korea) intravenously, while patients in the control group received 2 ml of normal saline intravenously. Anesthesia was induced via intravenous injection of propofol (1.5–2 mg/kg) and fentanyl (1–2 μg/kg). Orotracheal intubation was facilitated with an intravenous injection of rocuronium (0.6 mg/kg). Volume-controlled mechanical ventilation was initiated at a tidal volume of 8 ml/kg, respiratory rate of 12 breaths/min, and positive end-expiratory pressure of 5 cmH₂O; the target end-tidal carbon dioxide concentration of 30–40 mmHg was maintained by adjusting the respiratory rate. Anesthesia was maintained with oxygen and nitrous oxide (O₂:N₂O; 50:50) and desflurane (3–8 vol% end-tidal concentration) to keep the PSI at 25–50. At the end of surgery, a urinary catheter was placed by a urologist after lubrication with 2% lidocaine jelly (Instillagel®; Farco-Pharma GmbH, Germany). The size of the urethral catheter and volume of the balloon were at the discretion of the urologist. The balloons were filled with normal saline. At the end of surgery, and after confirming a TOF count of at least 2, all inhalation anesthetics were stopped and the neuromuscular block was reversed with 40–50 μg/kg neostigmine and 10 μg/kg glycopyrrolate. After confirming recovery of the neuromuscular block (TOF ratio ≥ 0.9), spontaneous respiration (respiratory rate > 12/min; tidal volume > 5 mg/kg), and PSI > 75, extubation was performed by an anesthesiologist. The time between stopping
the inhalation anesthetics and extubation was measured. EA was assessed after stopping the inhalation anesthetics until 5 min after extubation in the operating room, and between admission and discharge from the post-anesthesia care unit (PACU) using the Riker Sedation-Agitation Scale (RSAS; 1 = unarousable, 2 = very sedated, 3 = sedated, 4 = calm and cooperative, 5 = agitated and calm to verbal instructions, 6 = very agitated, requiring restraint, and 7 = pulling at the tracheal tube, trying to remove catheters, or striking the staff) [12]. The highest RSAS scores in the operating room and PACU were recorded; scores ≥ 5 was considered indicative of the presence of EA.

All patients were observed for at least 1 h in the PACU. Postoperative pain was rated using a numerical rating scale (NRS; 0 = no pain; 10 = worst pain imaginable). The incidence and severity of CRBD were assessed at 0, 1, 2, and 6 h after patient arrival in the PACU by an anesthesiology resident using a 4-point scale (none = patient did not complain of any CRBD symptoms even when asked, such as urge to urinate or discomfort in the suprapubic region; mild = complaint of CRBD symptoms only on direct questioning; moderate = spontaneous complaint of CRBD symptoms, without any behavioral responses, such as attempts to remove the urethral catheter, flailing limbs, loud complaints; severe = spontaneous complaint of CRBD symptoms with a behavioral response) [13–16]. The mild, moderate, and severe categories were all considered indicative of CRBD. If the patient required an analgesic due to postoperative pain or CRBD, 25–50 mg pethidine was administered intravenously. The RSAS was evaluated at the same time as CRBD. An RSAS score ≤ 3 was recorded as sedation. Adverse events during the first 6 h postoperatively were recorded and analyzed.

The primary endpoints were the incidence and severity of CRBD 0, 1, 2, and 6 h after the patient arrived in the PACU. The secondary endpoints were the incidence and severity of EA during emergence and recovery from anesthesia.

Statistical analyses

Previous studies have reported an incidence of CRBD between 65% and 80% at 0 h postoperatively, following reversal of neuromuscular blockade with glycopyrrolate and neostigmine [13,17]. Based on these studies, we assumed that the incidence rates of postoperative CRBD would be around 65% in the control group. With an effect size (h) of 0.662, a power of 0.8, α-value of 0.05 (two-sided), and allocation ratio of 1 : 1, a sample size of 42 patients per group was required to detect a 50% reduction in the incidence of CRBD after administering dexamethasone. Considering a 5% dropout rate, 45 patients were enrolled in each group.

Statistical analyses were performed using SPSS Statistics™ software (ver. 18.0 for Windows; IBM SPSS Inc., USA). The distribution of continuous variables was assessed with the Kolmogorov–Smirnov test; normally distributed variables were analyzed using Student’s t-test and non-normally distributed variables were analyzed using the Mann–Whitney U test. Categorical variables were analyzed using the χ² test, the χ² test for trends (linear-by-linear association), or Fisher’s exact, as appropriate. A P value < 0.05 was considered significant. Cohen’s effect sizes d and h were also used to compare continuous and categorical variables, respectively.

Results

A total of 98 patients were screened for inclusion in the study. Eight patients were excluded due to prostate hypertrophy (n = 3), OAB (n = 1), neuropsychological disorder (n = 1), or refusal to participate (n = 3). Thus, 90 patients were randomly allocated to one of the two groups and completed the study (Fig. 1). There were no differences in the demographic and operative data between the two groups (Table 1).

The incidence rates of CRBD in the control and dexamethasone groups were 28.9% and 15.6% at 0 h, 55.6% and 55.6% at 1 h, 57.8% and 46.7% at 2 h, and 53.3% and 51.1% at 6 h following
PACU admission, but the differences between the two groups were not significant (P = 0.128, 1.000, 0.291, and 0.833, respectively). There were no differences in the severity of CRBD, as assessed at 0, 1, 2, and 6 h after the patient arrived in the PACU, between the groups (P = 0.057, 0.357, 0.086, and 0.739, respectively) (Table 2).

The recovery and postoperative data are presented in Table 3. The incidence rates of EA in the control and dexamethasone groups were 15.6% and 6.7% in the operating room (P = 0.315), and 24.4% and 15.6% in PACU (P = 0.292), respectively. The severity of EA was not different between the two groups in the operating room or PACU (P = 0.157 and 0.228 in the operating room and PACU, respectively). In addition, time to extubation, the postoperative NRS pain score, and the requirement for analgesics were comparable between the groups (all P > 0.05).

Adverse events during 6 h postoperatively, including sore throat, hoarseness, dry mouth, nausea, vomiting, headache, dizziness, dyspnea, and sedation, were not significantly different between the groups (Table 4).

**Discussion**

This study assessed the effects of dexamethasone on CRBD and EA in patients who received a urinary catheter after urological surgery. Intravenous administration of dexamethasone (10 mg) before induction of anesthesia did not reduce the incidence or severity of CRBD at 0, 1, 2, and 6 h after urological surgery. In addition, dexamethasone did not affect the incidence or severity of EA evaluated in the operating room and PACU after surgery.

The clinical symptoms (discomfort in the suprapubic region, burning sensation in the urethra, urinary frequency, and urgency) of CRBD mimic those of OAB (urinary urgency with or without urge incontinence) [15]. In addition, the pathophysiology of CRBD and OAB is associated with contraction of the involuntary detrusor muscle [3]. In CRBD, the urinary catheter stimulates the afferent nerve of the bladder, leading to acetylcholine release and muscarinic receptor-mediated involuntary contraction of the detrusor smooth muscle of the bladder [18]; the detrusor muscle of the bladder contains several subtypes (M1–M5) of the muscarinic receptors, but the M2 and M3 receptors are predominant. The M1 and M3 receptors are present in a 3 : 1 ratio. A minority of M3 muscarinic receptors are primarily responsible for contracting the detrusor, whereas M2 muscarinic receptors contribute to indirect contractions and/or inhibit detrusor relaxation [19]. Obstruction of the urinary tract, injuries to the bladder mucosa, nerve stimulation, contraction of the detrusor muscle, and inflammatory mediators promote PG synthesis [16,20]. Inflammatory stimulation due to urinary bladder catheterization leads to an increase in

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**Table 1. Demographic and Operative Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 45)</th>
<th>Dexamethasone group (n = 45)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.4 ± 15.4</td>
<td>59.6 ± 9.0</td>
<td>0.053</td>
</tr>
<tr>
<td>Sex M/F (n)</td>
<td>24/21</td>
<td>22/23</td>
<td>0.673</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.8 ± 8.0</td>
<td>160.3 ± 8.7</td>
<td>0.383</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.2 ± 12.6</td>
<td>66.5 ± 14.2</td>
<td>0.913</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.2 ± 3.6</td>
<td>25.8 ± 4.3</td>
<td>0.474</td>
</tr>
<tr>
<td>ASA classification (n)</td>
<td></td>
<td></td>
<td>0.334</td>
</tr>
<tr>
<td>I/II/III</td>
<td>14/27/4</td>
<td>8/34/3</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td>0.843</td>
</tr>
<tr>
<td>Ureteroscopic litholapaxy</td>
<td>29 (64.4)</td>
<td>30 (66.7)</td>
<td>0.824</td>
</tr>
<tr>
<td>Sling operation</td>
<td>7 (15.6)</td>
<td>6 (13.3)</td>
<td>0.764</td>
</tr>
<tr>
<td>TURBT</td>
<td>6 (13.3)</td>
<td>7 (15.6)</td>
<td>0.764</td>
</tr>
<tr>
<td>Vesicolitholapaxy</td>
<td>1 (2.2)</td>
<td>0 (0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Hydrocele</td>
<td>2 (4.4)</td>
<td>2 (4.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>40.0 (27.5, 60.0)</td>
<td>55.0 (27.5, 90.0)</td>
<td>0.130</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>70.0 (55.0, 90.0)</td>
<td>85.0 (52.5, 120.0)</td>
<td>0.164</td>
</tr>
<tr>
<td>Fluids (ml)</td>
<td>200.0 (125.0, 200.0)</td>
<td>200.0 (150.0, 300.0)</td>
<td>0.352</td>
</tr>
<tr>
<td>Urinary catheter size (Fr)(n)</td>
<td>14/16/18/20/22</td>
<td>8/29/3/5/0</td>
<td>0.727</td>
</tr>
<tr>
<td>Catheter balloon volume (ml)</td>
<td>5 (5, 5)</td>
<td>5 (5, 5)</td>
<td>0.398</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number of patients, number (%), or median (Q1, Q3). ASA: American Society of Anesthesiologists, TURBT: transurethral resection of bladder tumors.
PGE₂ synthesis due to increased activation of COX-2, which may lead to the clinical symptoms of CRBD. Therefore, antimuscarinic agents (e.g., oxybutynin, butylscopolamine, tolterodine, and glycopyrrolate), analgesics with anticholinergic activity (e.g., nefopam, tramadol, dexmedetomidine, and ketamine), and COX inhibitors (paracetamol and ketorolac), which inhibit PG synthesis, have been studied and can reduce CRBD.

Dexamethasone, a drug that is commonly used during the perioperative period, decreased the release of acetylcholine in an in vivo study of airway parasympathetic neurons, by increasing mRNA expression of the M₂ receptor. Simultaneously, dexamethasone enhances the degradation of acetylcholine by increasing

### Table 2. Incidence and Severity of Postoperative CRBD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 45)</th>
<th>Dexamethasone group (n = 45)</th>
<th>Effect size ℓ</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>13 (28.9)</td>
<td>7 (15.6)</td>
<td>0.323</td>
<td>0.128</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>7 (15.6)</td>
<td>6 (13.3)</td>
<td>0.065</td>
<td>0.764</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (13.3)</td>
<td>1 (2.2)</td>
<td>0.449</td>
<td>0.110</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>1 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>25 (55.6)</td>
<td>25 (55.6)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>18 (40.0)</td>
<td>23 (51.1)</td>
<td>0.223</td>
<td>0.290</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (13.3)</td>
<td>2 (4.4)</td>
<td>0.324</td>
<td>0.266</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (2.2)</td>
<td>0 (0)</td>
<td>0.298</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>2 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>26 (57.8)</td>
<td>21 (46.7)</td>
<td>0.223</td>
<td>0.291</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mild</td>
<td>22 (48.9)</td>
<td>20 (44.4)</td>
<td>0.090</td>
<td>0.673</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (11.1)</td>
<td>1 (2.2)</td>
<td>0.381</td>
<td>0.203</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>6 h</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>24 (53.3)</td>
<td>23 (51.1)</td>
<td>0.044</td>
<td>0.833</td>
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<tr>
<td>Severity</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Mild</td>
<td>20 (44.4)</td>
<td>20 (44.4)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (8.9)</td>
<td>3 (6.7)</td>
<td>0.082</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are presented as number (%). CRBD: catheter-related bladder discomfort.

### Table 3. Recovery and Postoperative Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 45)</th>
<th>Dexamethasone group (n = 45)</th>
<th>Effect size ℓ or ℓ</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the operating room</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>6.0 (5.0, 8.0)</td>
<td>7.0 (5.5, 8.0)</td>
<td>0.313</td>
<td>0.298</td>
</tr>
<tr>
<td>EA (n)</td>
<td>7 (15.6)</td>
<td>3 (6.7)</td>
<td>0.288</td>
<td>0.315</td>
</tr>
<tr>
<td>RSAS (3/4/5/6/7) (n)</td>
<td>4/3/4/2/1</td>
<td>4/3/3/0/0</td>
<td>NA</td>
<td>0.157</td>
</tr>
<tr>
<td>In PACU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS pain score</td>
<td>0 (0, 3.0)</td>
<td>0 (0, 1.0)</td>
<td>0.274</td>
<td>0.408</td>
</tr>
<tr>
<td>EA (n)</td>
<td>11 (24.4)</td>
<td>7 (15.6)</td>
<td>0.221</td>
<td>0.292</td>
</tr>
<tr>
<td>RSAS (3/4/5/6/7) (n)</td>
<td>0/3/4/1/0</td>
<td>0/3/7/0/0</td>
<td>NA</td>
<td>0.228</td>
</tr>
<tr>
<td>In PACU and wards</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pethidine (mg)</td>
<td>0 (0, 25.0)</td>
<td>0 (0, 25.0)</td>
<td>0.170</td>
<td>0.424</td>
</tr>
<tr>
<td>Pethidine (n)</td>
<td>16 (35.4)</td>
<td>12 (26.7)</td>
<td>0.188</td>
<td>0.362</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), number (%), or number of patients. EA: emergence agitation, RSAS: Riker Sedation-Agitation Scale, NRS: numerical rating scale (0 = no pain, 10 = worst imaginable pain), NA: not applicable, PACU: post-anesthesia care unit.
Dexamethasone and bladder discomfort

Table 4. Adverse Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 45)</th>
<th>Dexamethasone group (n = 45)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sore throat</td>
<td>7 (15.6)</td>
<td>12 (26.7)</td>
<td>0.197</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>3 (6.7)</td>
<td>2 (4.4)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (13.3)</td>
<td>4 (8.9)</td>
<td>0.739</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (4.4)</td>
<td>3 (6.7)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (15.6)</td>
<td>4 (8.9)</td>
<td>0.522</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Sedation (RSAS score ≤ 3)</td>
<td>4 (8.9)</td>
<td>3 (6.7)</td>
<td>&gt; 0.999</td>
</tr>
</tbody>
</table>

Values are presented as number (%). RSAS: Riker Sedation-Agitation Scale.

Cholinesterase activity [7]. Dexamethasone also reduces the COX-2 transcription rate and inhibits COX activity and the release of COX-2 and PGE₂ [8]. Therefore, we expected dexamethasone to help reduce CRBD, but this was not observed. The reasons for the differences in our results and expectations are uncertain, but a few possible explanations are as follows. First, dexamethasone, a synthetic glucocorticoid, increases the glomerular filtration rate in both experimental animals and humans [21]. In an experimental study [22], dexamethasone significantly increased the urine output without activating the renin-angiotensin-aldosterone system. We speculate that the increase in urine output due to the diuretic effect of dexamethasone may have contributed to the induction of symptoms of CRBD, such as urinary urgency. Second, we used neostigmine and glycopyrrolate (10 μg/kg) to reverse the neuromuscular block caused by rocuronium. Glycopyrrolate is an anticholinergic agent with high affinity for the M1 receptor [23]. Injecting 0.3 mg glycopyrrolate before inducing anesthesia decreases the incidence and severity of CRBD in the PACU compared to saline [14]. In addition, 10 μg/kg glycopyrrolate administered after surgery decreases the early postoperative incidence and severity of CRBD compared to the anticholinergic agent atropine [13]. Compared to these studies [13,14], the dosage of glycopyrrolate in our study was larger or the same. In addition, the incidence of CRBD at 0 h and 1 h postoperatively in the control group (28.9% and 55.6%, respectively) was lower or comparable to that in the glycopyrrolate groups in a previous study (65% and 54%, respectively) [13]. Therefore, reducing the incidence and severity of CRBD in the control group after glycopyrrolate administration may have decreased the difference between the two groups in this study.

Sex (male), the diameter of the urinary catheter (≥ 18 Fr), and type of surgery (urological surgery, especially endourology and bladder resection) are independent risk factors for CRBD [2]. CRBD exacerbates postoperative pain and may increase the incidence of EA [1,2]. Risk factors of EA include male sex, obesity, pre-existing mental health problems, type of surgery (oral cavity surgery or otolaryngological surgery), longer duration of surgery, emergency operation, the presence of invasive devices (e.g., urinary catheter or endotracheal tube), CRBD, voiding urgency, postoperative pain, PONV, sore throat, history of substance dependence, and method of anesthesia (inhalation anesthesia) [5,6,10]. Although the pathophysiological mechanism of EA remains unknown, the mainstay of EA management is prevention by eliminating risk factors [5,6].

We administered fentanyl (1–2 μg/kg) during the induction of anesthesia to prevent hemodynamic instability due to tracheal intubation. The analgesic dosage of fentanyl is 1–1.5 μg/kg [24]. Fentanyl has a prophylactic effect, preventing sevoflurane- and desflurane-related EA [25]. CRBD is resistant to conventional analgesics, such as opioids [16]; thus, fentanyl may not affect CRBD. However, considering the pharmacokinetic properties of fentanyl (duration of action of 30–60 min, elimination half-life of 219 min) [24] and the duration of surgery in this study, fentanyl would have reduced EA of the control group so that there was no difference between the two groups in this study. It is also possible that there was no difference in EA between the two groups because dexamethasone did not reduce CRBD, postoperative pain, PONV, or sore throat, which are risk factors for EA.

This study had several limitations. First, as mentioned previously, glycopyrrolate used in this study may have affected the incidence and severity of CRBD. If anticholinergics such as glycopyrrolate were not used for reversal of a rocuronium-induced neuromuscular blockade using sugammadex, the effects of dexamethasone on CRBD could be more clearly evaluated. Considering the incidence of CRBD (28.9% and 15.6% in the control and dexamethasone groups, respectively) at arrival in the PACU and the effects of glycopyrrolate on CRBD, additional studies with larger sample sizes and different types of reversal drugs (e.g., sugammadex) are required. Second, the clinical effects of dexamethasone
are associated with the dose administered [26]. Therefore, the effect of dexamethasone at a dose > 10 mg on CRBD and EA is unknown, and further research is needed. Third, although there was no statistical difference, the type of surgery, sex, and diameter of the urinary catheter, which are risk factors for CRBD, were not the same in both groups, which may have affected the incidence and severity of CRBD. In addition, sex, type of surgery, sore throat, PONV, and postoperative pain are risk factors for EA and may have affected the incidence and severity of EA. Future studies controlling these factors are needed. Finally, as the sample size was calculated based on the incidence of CRBD, the secondary outcome variables, i.e., the incidences of EA in the operating room and PACU, had lower statistical power values of 0.27 and 0.18, respectively, and it is possible that a type II error occurred. Therefore, further research with greater numbers of subjects is necessary to confirm the statistical significance of the differences in EA between the groups.

In conclusion, intravenous administration of 10 mg dexamethasone before induction of anesthesia did not further decrease the incidence or severity of either CRBD or EA in patients undergoing urological surgery.

**Funding**

None.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

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Sung-Ae Cho (Formal analysis; Writing – original draft; Writing – review & editing)
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Seok-Jin Lee (Data curation; Investigation)
Tae-Yun Sung (Conceptualization; Formal analysis; Methodology; Supervision; Writing – original draft; Writing – review & editing)
Gwan Woo Ku (Conceptualization; Formal analysis)
Choon-Kyu Cho (Data curation; Investigation)
Young Seok Jee (Data curation; Investigation)

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https://doi.org/10.4097/kja.21284
Introduction

Laparoscopic gallbladder surgery is the preferred option to open surgical procedures owing to various advantages, including reduced bleeding, lower surgical site infection rates, decreased costs, shorter hospital stay, earlier return to the activities of daily living, and enhanced recovery [1,2]. Despite all the advantages of laparoscopic surgery, however, early postoperative pain can be uncomfortable and even lead to prolonged hospital stay [3]. Pain occurring after abdominal surgery is transmitted by the cutaneous branches of the thoracolumbar (T6–L1) nerves in the anterolateral region [4,5]. Multimodal regimens are used for postoperative analgesia after abdominal surgery, including laparoscopic cho-

Application of unilateral rhomboid intercostal and subserratus plane block for analgesia after laparoscopic cholecystectomy: a quasi-experimental study

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Background: Interfascial plane block can be used to treat postoperative pain after laparoscopic surgery. This study aimed to investigate the effect of ultrasound-guided unilateral rhomboid intercostal and subserratus plane (RISS) block after laparoscopic cholecystectomy on the amount of analgesic consumption.

Methods: Fifty patients who underwent laparoscopic cholecystectomy were included in this quasi-experimental study. Patients fulfilling the inclusion criteria were analyzed in two groups: RISS group (RISS block with 20 ml of 0.25% bupivacaine + intravenous patient-controlled analgesia [IV-PCA] tramadol [n = 25]); and Control group (IV-PCA tramadol [n = 25]). The primary outcome was the total amount of tramadol used over 24 h. Secondary outcomes included side effects, additional analgesic use, and postoperative pain (at rest and during activity) at 2, 6, 12, and 24 h according to numerical rating scale (NRS) scores.

Results: Postoperative tramadol consumption at 24 h was significantly lower in the RISS group than in the Control group (P < 0.001). Resting NRS scores at 2 h and 6 h were significantly lower in the RISS group. NRS scores during movement in the RISS group were significantly lower at 2, 6, and 12 h postoperatively. There was no statistically significant difference in the rate of side effects and additional analgesic use between the groups (P > 0.05).

Conclusions: Unilateral RISS block was an effective method for pain management after laparoscopic cholecystectomy and can be used as a part of multimodal analgesia.

Keywords: Analgesia; Bupivacaine; Laparoscopic cholecystectomy; Nerve block; Pain; Pain management; Postoperative pain; Ultrasonography.
lecystectomy. For this purpose, short-acting opioids, non-steroidal anti-inflammatory drugs, and regional anesthesia techniques are used alone and in combination.

The main causes of early pain after laparoscopic cholecystectomy are peritoneum and abdominal wall distension due to pneumoperitoneum and somatic pain at the trocar insertion site(s) [4,5]. Effective use of truncal blocks, such as the erector spinae plane or quadratus lumborum block, has been demonstrated in postoperative pain management in laparoscopic cholecystectomy [6–8]. The rhomboid intercostal and subserratus plane (RISS) block provides analgesia from the third to the 12th thoracic dermatomes and has been used in postoperative pain management for thoracic surgeries [7,8]. Although it is used for postoperative analgesia after upper abdominal surgery, there have been no adequate studies investigating the use of RISS blocks in laparoscopic cholecystectomy [7,8].

Theoretical target dermatomes (T3–T12) for the RISS block may include areas that cause pain in laparoscopic cholecystectomy operations, including trocar insertion sites. Several studies have suggested that incisional pain is more predominant than visceral pain during the first 48 h postoperatively [1,9]. Therefore, the present study aimed to evaluate the effect of unilateral RISS block on postoperative analgesic consumption in patients undergoing laparoscopic cholecystectomy.

**Materials and Methods**

**Patient selection**

A quasi-experimental study, involving 120 patients who underwent laparoscopic cholecystectomy between January 2018 December 2020, was conducted with approval of the institutional ethics committee of Bursa Yuksek Ihtisas Training and Research Hospital (IEC # 2020-01-19). Patients 20 to 65 years of age, with American Society of Anesthesiologists (ASA) physical status I and II, were included in the study. Individuals with bleeding disorders, mental incapacity, known allergy to local anesthetics, and body mass index (BMI) of ≥ 35 kg/m² were excluded. Informed consent was obtained from all participants included in the study. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and with the 2013 Helsinki Declaration and its later amendments or comparable ethical standards.

Fifty patients fulfilling the study criteria were included in the experimental group (RISS block and intravenous patient-controlled analgesia [IV-PCA]), tramadol administered [n = 25]) and the Control group (IV-PCA only; tramadol [n = 25]) using a non-probabilistic sampling method (Fig. 1).

**Surgical protocol**

**Anesthesia**

After routine monitoring in the operating room, general anesthesia was induced using fentanyl (1–2 µg/kg), propofol (1–2 mg/kg), and rocuronium (0.8–1 mg/kg). Anesthesia was maintained using inhaled sevoflurane (3–5%) and an air and oxygen mixture administered at a rate of 2.5–3 L/min. Fentanyl (1–2 µg/kg) was administered during the surgery if needed.

**Surgery**

The surgical procedure was performed by the same surgical team using the four-port technique. The four ports were placed through the umbilicus, epigastric place (under the xiphoidal process), right lateral subcostal position (the intersection point of the costal arch and anterior axillary line), and right subcostal-midclavicular line. The intra-abdominal pressure never exceeded 14 mmHg.

**Pain management**

Patients in the preoperative RISS block group underwent procedures with a linear probe (10–18 MHz, MyLab30; Esaote, Italy) in the lateral decubitus position under standard monitoring ASA in the block room, as previously described.
Rhomboid intercostal block

A high-frequency linear probe was placed in the sagittal plane to the medial border of the scapula and then rotated counterclockwise to acquire a paramedian sagittal oblique image 1–2 cm medial to the scapular edge. A 22-gauge, 100 mm block needle was inserted craniocaudally using an in-plane technique. After confirming the correct placement of the needle tip by hydrodissection, 10 ml of 0.25% bupivacaine was injected into the plane between the rhomboid major and intercostal muscles [7,8] (Fig. 2A).

Sub serratus block

The ultrasound probe was slid down inferolateral to identify the serratus anterior muscle at the level of T6–T9. After confirming the needle position, 10 ml of 0.25% bupivacaine was injected between the serratus anterior and intercostal muscles [7,8] (Fig. 2B). All patients received tenoxicam 20 mg intravenously 30 min before the end of the surgery. Postoperative pain management in the surgical ward was maintained using an IV-PCA device with the same setting for all patients. The PCA device delivered a 25 mg bolus dose of tramadol on demand (maximum dose, 400 mg/day), with a lock time of 30 min and no basal infusion. Paracetamol (1 g) was administered as rescue analgesia. Pain was assessed using a 10-point numerical rating scale (NRS), ranging from 0 (no pain) to 10 (worst pain imaginable).

Outcome measure

The primary outcome measure of the study was total tramadol consumption at 24 h postoperatively. Secondary outcome measures included assessment of the total amount of opioids administered intraoperatively, postoperative NRS scores at rest and during movement (2, 6, 12, and 24 h), sensorial dermatomal block level (30 min after block administration and at 2 h postoperatively), rescue analgesic consumption, and postoperative nausea and vomiting. During movement, the postoperative NRS scores were evaluated while coughing or performing in-bed movements at 2 h and after taking five steps forward at 6 h. Patients were asked if they experienced pain at the port sites 2 h postoperatively.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corp., USA) for Windows 2013 (Microsoft Corp., USA). Data normality was evaluated using the Kolmogorov-Smirnov test. The chi-squared test was used for inter-group comparisons of categorical data and the Mann-Whitney U test was used for continuous variables. Differences with P value of < 0.05 were considered to be statistically significant.

Power analysis

In previous studies, tramadol consumption at 6 h postoperatively was found to be 59.7 ± 13.7 mg in patients who used IV-PCA (tramadol) [10]. In this study, a 20% decrease in tramadol consumption at 6 h postoperatively was expected in the RISS block group. To obtain a study power of 85% (α = 0.05), 25 patients per group was required; as such, a total of 50 patients was calculated.

Results

Demographic variables are summarized in Table 1. There were
no statistically significant differences between the groups in terms of age, BMI, and surgery duration. Postoperative tramadol consumption at 24 h was significantly lower in the RISS group than in the Control group (89 mg [range, 50, 175 mg] vs. 142 mg [range, 5, 275 mg]; respectively, P < 0.001) (Fig. 3). Resting NRS scores at 2 h and 6 h postoperatively were significantly lower in the RISS group. There were no significant differences between the other measurements (Table 2). NRS scores during movement in the RISS group were significantly lower at 2, 6, and 12 h postoperatively (Table 3). There were no differences of intraoperative opioid requirements, postoperative nausea and vomiting, and additional analgesic consumption (paracetamol) (Table 4).

### Evaluation of RISS block levels

The preoperative sensory block level was tested according to the loss of sensation to cold 30 min after the RISS block using alcohol-soaked cotton swabs. Loss of sensation was achieved at the T4–T12 dermatomes in 5 patients, T5–T10 in 13, T6–T9 in 5, and T7–T10 in 2. Five patients underwent sensory blocks that reached the anterior midline (Fig. 4). Postoperative evaluation revealed that 10 patients experienced discomfort at the umbilical port insertion site, and 13 experienced pain at the epigastric port insertion site (Fig. 4).

### Discussion

The present study investigated the analgesic effect of unilateral RISS block after laparoscopic cholecystectomy and revealed less tramadol consumption in the RISS block group during the 24 h postoperative follow-up. The RISS block group demonstrated lower NRS scores at rest up to 6 h and lower NRS scores with movement at the 12 h follow-up.

Pain after laparoscopic cholecystectomy necessitates the use of multimodal analgesia methods due to its somatic and visceral components [1,9]. Visceral pain due to laparoscopic cholecystectomy emerges due to surgical manipulation of the pneumoperitoneum and gallbladder bed. Thus, visceral pain can be reduced

### Table 1. Comparison of Demographic Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RISS group (n = 25)</th>
<th>Control group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51.6 (36, 62)</td>
<td>51 (35, 65)</td>
<td>0.784</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 (21.6, 28.0)</td>
<td>23.4 (21.3, 27.3)</td>
<td>0.234</td>
</tr>
<tr>
<td>Sex M/F n(%)</td>
<td>17 (68)/8 (32)</td>
<td>15 (60)/10 (40)</td>
<td>0.769</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or number (%). RISS: rhomboid intercostal and subserratus plane, BMI: body mass index.

### Table 2. Comparison of NRS Scores at Rest between the Groups

<table>
<thead>
<tr>
<th>NRS (at rest)</th>
<th>RISS group (n = 25)</th>
<th>Control group (n = 25)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 h</td>
<td>1.7 (0, 6)</td>
<td>2.7 (1, 6)</td>
<td>0.004†</td>
</tr>
<tr>
<td>6 h</td>
<td>1.6 (0, 5)</td>
<td>2.5 (1, 6)</td>
<td>0.022†</td>
</tr>
<tr>
<td>12 h</td>
<td>1.96 (0, 5)</td>
<td>2 (1, 6)</td>
<td>0.635</td>
</tr>
<tr>
<td>24 h</td>
<td>0.96 (0, 6)</td>
<td>1 (1, 6)</td>
<td>0.621</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). *Mann-Whitney U test for the inter-group comparisons. Values marked with † indicate statistically significant differences (i.e., P < 0.05). RISS: rhomboid intercostal subserratus plane, NRS: numerical rating scale.

### Table 3. Comparison of NRS Scores on Movement between Groups

<table>
<thead>
<tr>
<th>NRS (on movement)</th>
<th>RISS group (n = 25)</th>
<th>Control group (n = 25)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 h</td>
<td>2.7 (0, 6)</td>
<td>5.1 (3, 7)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>6 h</td>
<td>2 (0, 5)</td>
<td>4 (0, 7)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>12 h</td>
<td>1.8 (0, 3)</td>
<td>3.2 (0, 6)</td>
<td>0.014†</td>
</tr>
<tr>
<td>24 h</td>
<td>1.9 (0, 4)</td>
<td>1.9 (0, 5)</td>
<td>0.861</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). *Mann-Whitney U test for the inter-group comparisons. Values marked with † indicate statistically significant differences (i.e., P < 0.05). RISS: rhomboid intercostal subserratus plane, NRS: numerical rating scale.

### Table 4. Side Effects, Additional Analgesic Requirement(s), Duration of Surgery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RISS group (n = 25)</th>
<th>Control group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative nausea and vomiting</td>
<td>–</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>Additional analgesic requirement(s) (n)</td>
<td>1</td>
<td>3</td>
<td>0.186</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>51 (40, 67)</td>
<td>49 (40, 60)</td>
<td>0.497</td>
</tr>
<tr>
<td>Opioid administered during surgery (µg)</td>
<td>76 (60, 110)</td>
<td>81 (60, 150)</td>
<td>0.726</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), or numbers. RISS: rhomboid intercostal and subserratus plane.

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Fig. 3. Total tramadol consumption at 24 h postoperatively. RISS: rhomboid intercostal and subserratus plane.

https://doi.org/10.4097/kja.21229

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with shorter surgery times and creating a pneumoperitoneum with lower pressure [11]. However, somatic pain due to trocar entry incisions has been suggested to be the main cause of early pain after laparoscopic gallbladder surgery [9].

The rhomboid intercostal block has previously been used for pain management in thoracic wall surgery. However, it was later modified by Elsharkawy et al. [7,8,12] and used together with the subserratus plane block in the treatment of post-abdominal surgery pain, and the combination of the two blocks was subsequently renamed the “RISS block”. RISS block using 30 ml of local anesthetic has been successfully used in transapical transcatheter aortic valve implantation [13]. In another case series, RISS block using 20 ml of local anesthetic was used for pain management for multiple rib fractures, and the authors indicated that local anesthetic could spread to the ventral and dorsal radices of the intercostal nerves [14]. Elsharkawy et al. [7] described RISS blocks performed on 6 fresh non-embalmed cadavers and on 15 live patients with different indications, including upper abdominal surgeries. They demonstrated that the lateral branches of the intercostal nerves were dyed from T4 to T8 in all cadavers and, in the clinical part of their study, they observed that the most cephalo-caudal extent of the sensory loss to cold was from T2 to T12 [7]. In a study involving 21 patients undergoing abdominal surgery, RISS blocks provided analgesia at dermatomes varying from T3 to T12 with a high patient satisfaction rate [8].

The nerves targeted by the RISS block include the lateral cutaneous branches of the ventral branches of the thoracic intercostal nerves, located between the rhomboid muscle and the intercostal muscles, and deep into the scapula serratus anterior muscle. In addition, it has been reported that 2 different mechanisms may be operative during analgesia. First, local anesthetic agents may affect the dorsal rami of the thoracic intercostal nerves at the point where the erector spinae muscle originates from the thoracic transverse processes at the level of T3–T9 through medial spread in the tissue plane. Second, the authors hypothesized that local anesthesia may also spread into the paravertebral space because of its spread under the erector spinae muscle [8].

In our study, the dermatomal coverage of RISS blocks was consistent with the literature. The most cephalad extent of the block was T4, and the most caudal extent was the T12 dermatome. Sensory loss was present in the medial and lateral areas, whereas only five patients experienced a sensory block at the midline of the abdominal wall. A limited number of studies have reported the efficacy of unilateral regional blocks after laparoscopic abdominal surgeries. In another study, subcostal transversus abdominis plane blocks were found to result in significantly lower postoperative opioid consumption than local anesthetic infiltration to port sites after laparoscopic cholecystectomy [15].

In the present study, unilateral RISS blocks were effective in reducing pain scores and opioid consumption after laparoscopic surgery. RISS blocks appear to be good choices as part of a multimodal analgesia regimen for both thoracic and upper abdominal surgeries. Compared with central blocks, RISS blocks are less invasive and associated with fewer complications such as nerve damage, hemodynamic instability, and bleeding [8].

The broadest analgesic efficacy detected for the RISS block was between the T3 and T12 dermatomes. Trocar insertion sites for laparoscopic cholecystectomy concern the T6 and T10 dermatomes. It was believed that analgesia could be provided in these dermatomes using the RISS block. In addition, we believe that the potential mechanisms of action of RISS block, such as the paravertebral spread of local anesthetics, ventral rami blockade of intercostal nerves, and neuronal structures in the anatomical structure of the fascia, which we have attempted to address in the study, may be effective for analgesia. Several reports have commented on the RISS block mechanism; however, its paravertebral extension remains controversial. A notable result of the present study was that five patients experienced sensory blocks extending to the abdominal midline. Nevertheless, except for these 5 patients in the RISS block group, 10 patients with no sensory block in the midline were not troubled by pain from the umbilical port site. We believe this may be due to the anatomical structure of the fascia, which is considered to play a role in the efficacy of interfascial blocks. It is believed that, apart from the intercostal nerve block, the sensory innervation of the fascia and the presence of sympathetic nerve endings may play a role in the efficacy of interfascial blocks [16,17]. Animal studies have immunohistochemically identified free nerve endings of the thoracolumbar fascia and the presence of Ruffini and Pacinian corpuscles [18]. Another animal study found that dorsal horn neurons became prominent after
stimulation of these receptors, and a different study involving hu-
mans found that interfascial injection of saline (0.9%) created
burning and throbbing-like symptoms known to be transmitted
by A- and C-fiber nociceptors [19,20]. Similar results and consid-
erations have been shared in studies using the interfascial injec-
tion technique for the treatment of myofascial pain syndrome
[21–23]. Stecco et al. [24] described the proprioception and noc-
ception properties of the fascial system through Aδ, C, and post-
ganglionic sympathetic fibers. Despite the limited literature, the
current data indicate that the anatomical structure of the fascia
may play a role in the efficacy of interfascial blocks.

The present study was limited by its lack of randomization
and the small cohort of subjects. Additionally, no adjuvant drugs were
used. RIß block procedures are new techniques; as such, long-
term follow-up data remain lacking. Although there are published
studies that have used adjuvants, we did not add adjuvants to local
anesthetic drugs in the present study because they were not used in
our clinical practice.

In conclusion, unilateral RIß block was an effective method for
pain management after laparoscopic cholecystectomy and may be
used as a component of multimodal analgesia regimens.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was re-
ported.

Author Contributions

Korgün Ökmen (Conceptualization; Data curation; Investigation;
Methodology; Writing – original draft)
Hande Gürbüz (Supervision; Writing – review & editing)
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With the advent of wearable devices capable of easily measuring patients’ respiratory rate, heart rate (HR), and heart rate variability (HRV), early signs of illness can potentially be identified. Patients’ respiratory and HR are typically elevated by illness, whereas HRV is generally decreased [1].

Smart watches and wristbands are important accessories for fitness, but their application in healthcare is still in its early stages. Tanwar et al. [2] hypothesized that a consistent decline in the values of major HRV components could be attributed to the onset or worsening of SARS-CoV-2 infections.

Hasty et al. [3] reported that substantial decreases in HRV preceded elevations in C-reactive protein (CRP) levels in the ensuing 72 hours with a 90.9% positive predictive value and a 0.187 error rate (sensitivity: 83.3% and specificity: 75%). The ability to detect an early increase in the inflammatory response might prove to be vital for mitigating the deleterious effects of Coronavirus disease 2019 (COVID-19) over time. These authors demonstrated the potential value of short-segment intermittent HRV analyses in this patient population. However, there are very few studies in the literature related to HRV in patients with COVID-19, even though HRV has been identified as a useful noninvasive method for monitoring the clinical evolution of COVID-19.

Background: To detect an early increase in the inflammatory response might prove to be vital for mitigating the deleterious effects of the disease over time.

Case: A 52-year-old obese man with moderate asthma and hypertension, who developed COVID-19 and had moderate symptoms, used a wearable device to record heart rate variability (HRV) during his illness. He had low parasympathetic tone, which decreased daily until it reached almost 2 standard deviations (SD) below normal values at the end of the second week. His sympathetic tone increased from > 3 SD to > 5 SD.

Conclusions: These findings suggest an altered modulation of the sympathetic and parasympathetic nervous systems in COVID-19, such that the sympathetic tone is augmented and the parasympathetic tone is reduced. Population norms of COVID-19 infections should be further studied over the short-term and using 24 h HRV measurements.

Keywords: Ambulatory monitoring; Autonomic nervous system; Computer-assisted signal processing; COVID-19; Heart rate; Wearable electronic devices.

Heart rate variability follow-up during COVID-19 -a case report-

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With the advent of wearable devices capable of easily measuring patients’ respiratory rate, heart rate (HR), and heart rate variability (HRV), early signs of illness can potentially be identified. Patients’ respiratory and HR are typically elevated by illness, whereas HRV is generally decreased [1].

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In a prospective observational pilot study, Aragón-Benedí et al. [4] hypothesized that a depletion of the sympathetic nervous system and a predominance of parasympathetic activity reflected a compensatory anti-inflammatory response in severely ill COVID-19 patients.

We report the case of a 52-year-old patient with moderate asthma, hypertension, and obesity and a surgical history of a total thyroidectomy many years prior for a benign colloid goiter, who developed COVID-19 with moderate symptoms without the need for hospitalization. He used a wearable device (Polar 7°, developed by Polar Electro on 2007, USA) connected to a mobile application (CardioMood®, developed by CardioMood SA, Switzerland) to monitor HRV during his illness.

### Case Report

During the last few days of August 2020, the patient began experiencing symptoms and tested positive for COVID-19 using reverse transcription polymerase chain reaction. His symptoms started with fatigue, headache, body ache, and fever at approximately 38°C, followed by sore throat and congestion. He went to the hospital and was advised to maintain home isolation (Fig. 1). On the second day after the onset of symptoms, he lost his sense of smell and taste, had an immediate loss of appetite, and developed diarrhea. During the first week, all symptoms remained stable. By the morning of the sixth day, his fever had resolved. He had a fever relapse on day 7, along with extreme fatigue and diahragmatic findings. CRP was 23 mg/L, blood oxygen saturation was 90%, neutropenia, right middle lobe pneumonia, and oxygen therapy was initiated. By day 10, his symptoms were resolved.

**Fig. 1.** Patient clinical course. HRV was recorded from day 8 to 12 when symptoms worsened and the last record was on day 19, when the patient had almost recovered. CRP: C-reactive protein.
rhea. By day 10, he developed wheezing and shortness of breath, which were evaluated in a hospital. Chest radiography showed an opacity in his right lung, his SaO₂ was 90%, and his laboratory results were altered, showing neutropenia and high CRP levels. He resumed his scheduled asthma treatment, though he was non-compliant and experienced multiple exacerbations. On day 11, his feet felt cold, and he reported paresthesia. He had a persistent fever of approximately 38°C. On day 12, his fever resolved spontaneously, and hospital admission was therefore not necessary.

He began monitoring his HRV during the second week of his illness, with a chest band device for HR monitoring (Polar 7™, developed by Polar Electro on 2007, USA). He had a mobile application and was able to obtain inter-beat intervals between all successive heartbeats (RR intervals). This device has been used for monitoring athlete training and have recently been validated for use in healthcare [5].

We obtained raw data (RR intervals) from measurements obtained during the second week of the patient’s illness, when he had already been diagnosed with unilateral SARS-CoV-2 pneumonia, with a low-grade fever of approximately 38°C and an oxygen saturation of approximately 90%. Measurements were conducted at rest in the afternoon from days 8 to 12. Another measurement was performed a week later when home isolation was discontinued. The mobile application was used only for data collection. The Kubios® (Kubios Oy, Finland) standard software [6] (https://pubmed.ncbi.nlm.nih.gov/24054542/, cited by 458 articles by 2021) and ARTiiFACT® (developed by Tobias Kaufmann, Germany) software [7] (https://pubmed.ncbi.nlm.nih.gov/21573720/, cited by 74 articles by 2021), which have been cited by multiple previous reports, were used for HRV data analysis, and both yielded similar results. We also performed time-domain analysis using Python scripts to validate the results and to perform a visual exploratory analysis, plotting circles with the intent of showing the sympathetic nervous system (SNS) tone variations for each day. The working IPython notebook is available from https://colab.research.google.com/drive/1qcL2tdfrlejoXjsKVWQW9IEr-4Hxj0iR?usp=sharing.

Normal distributions of data from each sample were tested and QQ plots (quantile-quantile: standard distribution quantiles vs. sample quantiles plot) were drawn using the ARTiiFACT® software (Fig. 2). All patient samples appeared to follow a normal Gaussian distribution, except for the sample from day 19, when it appears to be skewed to the left. This might have been caused by an artifact in the first few seconds of the sample (Fig. 3, day 19 sample).

The time series graphs of the RR intervals for each sample are shown in Fig 3. The differences between the ill and normal states are immediately evident. The RR intervals were higher when the patient recovered.

Discussion

HRV is defined as the variation in the elapsed time between consecutive heartbeats, measured in milliseconds. A person’s HRV is governed by two aspects of the autonomic nervous system: the sympathetic and parasympathetic branches [8].

The sympathetic branch regulates the body’s reactions to mental and physical stress by releasing suitable hormones, thereby causing an increase in heart contractions and reducing HRV. Its counterpart, the parasympathetic branch, regulates the body when it must recover from a stressful state. To do this, the parasympathetic branch slows down the HR and thus increases HRV. Studies have shown that HRV can be used to predict morbidity caused by mental disorders such as depression and posttraumatic stress disorder or physical afflictions such as diabetes, concussions, and asthma. [9] Therefore, HRV is a good indicator of underlying health issues and is an important factor that can be used to reduce the likelihood of mortality.

Kleiger et al. [10] published a milestone study in the late 1980s that established HRV as an independent predictor of mortality in patients with acute myocardial infarction. For a historical perspective of HRV, refer to the comprehensive review conducted by Nicolini et al. [11].

In 1996, a consensus statement was issued by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, specifying standards of measurement for time- and frequency-domain measures [12], providing a summary of the main HRV measures, and discussing methods of evaluation, duration of electrocardiogram (ECG) recording, and nomenclature. The duration of the recordings included in this case report was 2 min. There is evidence in the literature that 3 min recordings should be used for time- and frequency-domain methods, and 2 min recordings can be used for frequency-domain methods alone, although the task force recommended 5 min recordings. Recordings < 2 min are considered ultrashort.

The discussion of HRV measurements has been centered on a reductionistic model of sympathovagal balance between the parasympathetic nervous system (PNS) and the SNS. The application of nonlinear dynamics to HRV calculations produces nonlinear measurements that might best capture system complexity. It is widely accepted that the SNS tone has an arrhythogenic and pro-ischemic effect, while the PNS is protective. The concept of
autonomic modulation in a complex system is gaining support, although we will use a reductionist model centered on the autonomic tone and the heart to interpret our findings given the small number of measurements in this study. Time-domain calculations are used to quantify the variability between inter-beat intervals.

Optimal HRV is associated with health, adaptability, and resilience. HRV declines with age and increases with increased aerobic fitness. Women show relative PNS dominance, while men show relative SNS dominance. Autonomic nervous system dysfunction is a common systemic indicator of poor health [13].
Table 1 summarizes all our time-domain calculations using the ARTiiFACT® software. The mean RR interval shows parasympathetic cardiac activation when its value is higher. When actively ill with COVID-19, our patient had lower discharge values. All samples taken during the patient's COVID-19 illness had similar mean RR intervals.

Results were similar regarding the root mean square of successive differences between RR intervals (RMSSD). This measurement reflects the beat-to-beat variation in HR, which is less influenced by respiratory sinus arrhythmia (RSA) than other time-domain parameters supposed to index vagal tone, and is used to estimate PNS-mediated changes in HRV. Our patient had...
Table 1. Time and Frequency Domain Analysis Results Using ARTiiFACT Software

<table>
<thead>
<tr>
<th>Parameters (unit)</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 12</th>
<th>Day 19</th>
<th>Reference values [14]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RR (ms)</td>
<td>829.64</td>
<td>824.55</td>
<td>753.24</td>
<td>689.22</td>
<td>1083.01</td>
<td>Mean</td>
</tr>
<tr>
<td>Median RR (ms)</td>
<td>829.00</td>
<td>824.00</td>
<td>754.00</td>
<td>687.00</td>
<td>1090.00</td>
<td>Median</td>
</tr>
<tr>
<td>Mean HR (bpm)</td>
<td>72.32</td>
<td>72.77</td>
<td>79.66</td>
<td>87.05</td>
<td>55.40</td>
<td>Mean</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>18.72</td>
<td>13.10</td>
<td>8.66</td>
<td>14.61</td>
<td>66.80</td>
<td>Mean</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>9.27</td>
<td>8.87</td>
<td>4.91</td>
<td>5.84</td>
<td>36.92</td>
<td>Mean</td>
</tr>
<tr>
<td>NN50 (ms)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>23.00</td>
<td>Median</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>20.72</td>
<td>Median</td>
</tr>
<tr>
<td>VLF (%)</td>
<td>59.38</td>
<td>63.14</td>
<td>40.89</td>
<td>43.34</td>
<td>56.49</td>
<td>Median</td>
</tr>
<tr>
<td>LF (%)</td>
<td>30.93</td>
<td>21.15</td>
<td>44.45</td>
<td>47.41</td>
<td>11.73</td>
<td>Median</td>
</tr>
<tr>
<td>HF (%)</td>
<td>9.69</td>
<td>15.72</td>
<td>14.66</td>
<td>9.24</td>
<td>31.78</td>
<td>Median</td>
</tr>
<tr>
<td>LF/HF (%)</td>
<td>3.19</td>
<td>1.35</td>
<td>3.03</td>
<td>5.13</td>
<td>0.37</td>
<td>Mean</td>
</tr>
<tr>
<td>LF [n.u.]</td>
<td>76.14</td>
<td>57.36</td>
<td>75.20</td>
<td>83.69</td>
<td>26.97</td>
<td>Mean</td>
</tr>
<tr>
<td>HF [n.u.]</td>
<td>23.86</td>
<td>42.64</td>
<td>24.80</td>
<td>16.31</td>
<td>73.03</td>
<td>Mean</td>
</tr>
<tr>
<td>VLF [abs] (ms²)</td>
<td>349.63</td>
<td>127.79</td>
<td>29.09</td>
<td>93.47</td>
<td>1250.27</td>
<td>Mean</td>
</tr>
<tr>
<td>LF [abs] (ms²)</td>
<td>182.10</td>
<td>42.80</td>
<td>31.62</td>
<td>102.25</td>
<td>259.70</td>
<td>Mean</td>
</tr>
<tr>
<td>HF [abs] (ms²)</td>
<td>57.08</td>
<td>31.81</td>
<td>10.43</td>
<td>19.93</td>
<td>703.39</td>
<td>Mean</td>
</tr>
<tr>
<td>Recording length (s)</td>
<td>118.64</td>
<td>120.39</td>
<td>120.52</td>
<td>120.61</td>
<td>120.21</td>
<td>Mean</td>
</tr>
</tbody>
</table>

Absolute power is calculated as ms squared divided by cycles per second (ms²/Hz) and relative power is estimated as the percentage of total HRV power or in normal units (nu), which divides the absolute power for a specific frequency band by the summed absolute power of the LF and HF bands. This allows for a direct comparison of the frequency-domain measurements of two clients despite a wide variation in specific band power and total power among healthy, age-matched individuals. Inter-beat interval: time interval between successive heartbeats, NN intervals: inter-beat intervals from which artifacts have been removed, RR intervals: inter-beat intervals between all successive heartbeats, SD: standard deviation, HR: heart rate, SDNN: standard deviation of NN intervals, RMSSD: root mean square of successive interval differences, NN50: number of adjacent NN intervals that differ from each other by more than 50 ms (requires a 2-min epoch), pNN50: percentage of adjacent NN intervals that differ from each other by more than 50 ms, VLF: relative power of the very low-frequency band (0.0033–0.04 Hz), LF: relative power of the low-frequency band (0.04–0.15 Hz), HF: relative power of the high-frequency band (0.15–0.4 Hz), LF/HF: ratio of LF-to-HF power, LF [n.u.]: relative power of the very-low-frequency band (0.0033–0.04 Hz), HF [n.u.]: relative power of the low-frequency band in normal units, HF [n.u.]: relative power of the high-frequency band in normal units, VLF [abs]: absolute power of the very-low-frequency band, LF [abs]: absolute power of the low-frequency band, HF [abs]: absolute power of the high-frequency band.

Because it is influenced by RSA. It reflects PNS activity but cannot be considered a pure index of cardiac vagal control. It is highly correlated with time-domain measures, such as the RMSSD and the proportion of successive NN intervals > 50 ms (pNN50). Lower power of HF is correlated with stress, anxiety, or worry. The LF/HF ratio might be related to the SNS and PNS ratio, with a lower ratio reflecting PNS dominance and a higher ratio reflecting SNS dominance. Since this is a reductionist approach to the complex relationship between SNS and PNS, this assumption may be controversial. Our patient had higher LF values than HF values during his COVID-19 illness. The relationships between these two frequency-domain measurements are graphically summarized in Fig. 4. It is evident that the relationship was completely inverted when the patient had recovered.

Time-domain norms have been reviewed in previous short-term HRV studies and 24-h measurements [14]. These norms are used by the Kubios© software (developed by Kubios Oy, founded in 2016 in Kuopio, Finland as a spin-off company from University of Eastern Finland) to report results (Fig. 5). Our patient had a lower RMSSD when ill than when he had recovered. Our patient also had a lower standard deviation (SD) of normal-to-normal (NN) intervals (SDNN), which is the “gold standard” for medical stratification of cardiac risk since it is more accurate when calculated over a 24 h period. SDNN values < 50 ms are unhealthy or high risk, those between 50 and 100 ms indicate moderate risk, and values > 100 ms are considered normal. For short-term recordings taken at rest, the primary source of these variations is parasympathetically mediated respiratory baroreflex activity.

Frequency-domain measurements are used to estimate the distribution of the signal energy within four frequency bands, and are expressed as the relative or absolute power. The low-frequency band (LF: 0.04–0.15 Hz) is called the baroreceptor band because it reflects baroreceptor activity at resting conditions and is also influenced by low respiratory rates or deep breathing. The high-frequency band (HF: 0.15–0.40 Hz) is known as the respiratory band because it is influenced by RSA. It reflects PNS activity but cannot

https://doi.org/10.4097/kja.21338
Fig. 4. Exploratory analysis PNS (orange) vs. SNS (blue). PNS: parasympathetic nervous system, SNS: sympathetic nervous system, LF: low-frequency band (0.04–0.15 Hz), HF: high-frequency band (0.15–0.40 Hz). Day 8 to 12 SNS (blue outer circle) predominates over PNS (orange inner circle) when the patient was in stage II of Covid-19 (Fig. 1). Day 19 shows otherwise, a higher parasympathetic activity, although it might also be due to sympathetic depletion [4].
(A) Day 8 (fever, fatigue, lack of smell and taste, diarrhea)

![Kubios HRV - Results compared to normal (resting) values](image)

Parasympathetic nervous system (PNS)
- Mean RR: 830 ms
- RMSSD: 9.3 ms
- SD1: 20.4 %

SNS index = -1.45

B) Day 9 (fever, fatigue, lack of smell and taste, diarrhea)

![Kubios HRV - Results compared to normal (resting) values](image)

Parasympathetic nervous system (PNS)
- Mean RR: 825 ms
- RMSSD: 8.3 ms
- SD1: 26.5 %

SNS index = 4.57

(C) Day 10 (fever, worsening of symptoms, hospital visit: CRP = 23 mg/L, SaO₂ =90%, neutropenia, right middle lobe pneumonia)

![Kubios HRV - Results compared to normal (resting) values](image)

Parasympathetic nervous system (PNS)
- Mean RR: 73 ms
- RMSSD: 35.4 ms
- SD1: 73.5 %

SNS index = 7.71 %

(D) Day 12 (fever, extreme fatigue, shortness of breath, wheezing)

![Kubios HRV - Results compared to normal (resting) values](image)

Parasympathetic nervous system (PNS)
- Mean RR: 87 bpm
- RMSSD: 34.1 bpm
- SD1: 83.0 %

SNS index = -2.22

(E) Day 19 (recovered)

![Kubios HRV - Results compared to normal (resting) values](image)

Parasympathetic nervous system (PNS)
- Mean RR: 56 bpm
- RMSSD: 12.0 bpm
- SD1: 77.0 %

SNS index = 0.44

Fig. 5. Time-domain results using Kubios® software (2 min measurements). RR: interbeat intervals between all successive heartbeats, SD: standard deviations, HR: heart rate, RMSSD: root square of successive interval differences, PNS: parasympathetic branch of the nervous system, SNS: sympathetic branch of the nervous system, SD1: standard deviation (hence SD) of the distance of each point from the y = x = average RR interval, along the line of identity. Kubios software was developed by Kubios Oy, founded in 2016 in Kuopio, Finland as a spin-off company from University of Eastern Finland.
**Day 19**

**Nonlinear results**

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* Results are calculated from the non-detrended selected RR series.

**Day 9**

**Nonlinear results**

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* Results are calculated from the non-detrended selected RR series.

**Day 12**

**Nonlinear results**

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* Results are calculated from the non-detrended selected RR series.

**Day 10**

**Nonlinear results**

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* Results are calculated from the non-detrended selected RR series.

**Day 8**

**Nonlinear results**

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* Results are calculated from the non-detrended selected RR series.

---

Fig. 6. Kubios®: Nonlinear Results. SD1, standard deviation (hence SD) of the distance of each point from the y = x axis, perpendicular to the line of identity; SD2: standard deviation of each point from the y = x + average RR interval, along the line of identity; Kubios software was developed by Kubios Oy, founded in 2016 in Kuopio, Finland as a spin-off company from University of Eastern Finland.
low parasympathetic tone during his COVID-19 illness, which decreased every day until it reached almost 2 SDs lower than normal at the end of the second week. Conversely, his sympathetic tone was very high and reached at > 3 SDs up to > 5 SDs from normal values. These results suggest that an alteration in the modulation of the SNS and PNS occurred, which apparently augmented sympathetic tone and decreased parasympathetic tone. The clinical value of short-term measurements of HRV in COVID-19 patients is yet to be established. However, in an observational pilot study of patients with COVID-19 on mechanical ventilation, Aragón-Benedi et al. [4] found that the normalized high frequency component (HFnu) was higher in the non-survivor group and was correlated with higher IL-6 levels. A cut-off value of 80 predicted mortalities with a sensitivity of 100%, specificity of 85.7%, positive predictive value of 87.5%, and negative predictive value of 100% was found. The non-survivor group had values > 80. The receiver operating characteristic curve demonstrated that the HFnu could predict mortality with an area under the curve of 0.980. Our patient had surpassed the threshold of 80 on day 12, although he did ultimately recover.

The medical stratification of cardiac risk was performed using 24 h HRV recordings. The results from the recordings that were < 5 min in length should be interpreted with caution and should not be compared with long recordings. The patient’s values returned to normal one week after home isolation was discontinued (Fig. 5E).

Nonlinear measurements index the unpredictability of a time series. The Poincaré plot is a scatter plot of the RR interval against the prior interval. The area of the ellipse is the total HRV and is correlated with the baroreflex sensitivity, LF and HF power bands, and RMSSD. Researchers use it to visually search for patterns hidden within a time series. The SD of the distance of each point from the y = x axis, perpendicular to the line of identity (SD 1), and the SD of each point from the y = x + average R–R interval, along the line of identity (SD 2) values were much lower during the patient’s illness than after recovery (Fig. 6). The SD 1/SD 2 ratio correlated with the HF/HR ratio.

Although we were able to obtain raw data from the CardioMood website (https://www.cardiomood.com/), we could only obtain the RR interval time series. Since we did not determine the sampling frequency rate, we were not able to replicate the same results using the RHRV package in R commander. The device we used was a photoplethysmography-based (PPG) biosensor, which is less accurate than ECG-based biosensors. Data were captured over a short period lasting 120 s, and the frequency-domain analyses may have been inaccurate for measurements < 300 s. According to Laborde et al. [15], a 5-min recording is recommended, when possible, as it enables comparisons between clinical studies. Short-term values are only appropriate when a patient is breathing at a normal rate (11–20 bpm); however, we could not obtain data regarding the respiratory rate of our patient [13].

The value of HRV as a predictor of COVID-19 mortality is yet to be established. If HRV is considered a marker of autonomic nervous system modulation, the influence of erratic rhythm should be considered because it affects short-term time- and frequency-domain measures. Nonlinear measurements of HRV can detect a decrease in autonomic nervous system modulation and loss of complexity, which might imply a worse prognosis. Population norms should be further studied for patients with COVID-19 using short-term and 24 h HRV measurements. ECG-based wearable devices have been shown to be more accurate for HRV calculations than PPG-based devices, and some have been validated for clinical use [5]; therefore, we recommend their use in patients with COVID-19. These devices are widely available at a low cost and can be used to monitor the clinical evolution of patients with COVID-19 who are isolated at home. In desperate circumstances, where there is an insufficient number of hospital beds, this method might be useful for anticipating worsening symptoms and for admitting only those patients at risk of developing severe COVID-19 to the hospital. We strongly recommend further explorations of HRV in the COVID-19 population.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Alejandro Figar Gutiérrez (Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Software; Writing – original draft; Writing – review & editing)
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Francisco O. Redelico (Conceptualization; Methodology; Writing – review & editing)
Maria de Los Angeles Iturralde (Conceptualization; Writing – original draft; Writing – review & editing)
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15. Laborde S, Mosley E, Thayer JF. Heart rate variability and cardiac vagal tone in psychophysiological research - recommendations for experiment planning, data analysis, and data reporting. Front Psychol 2017; 8: 213.
Shoulder joint surgery is associated with severe postoperative pain, and continuous interscalene brachial plexus block (cISBPB) using a catheter is an effective treatment modality. Despite proper catheterization, cases of cISBPB with inadequate postoperative analgesia in the brachial plexus innervation area are occasionally encountered. Several studies have been conducted in an effort to reduce inadequate analgesia, such as the comparison of catheter insertion approaches \[1–3\]; however, there is no consensus on the best approach. Inadequate analgesia may be associated with postoperative catheter tip dislocation from the interscalene groove, which occurs during and after surgery. The frequency of catheter dislocation has been reported \[4\], and Aoyama et al. \[5\] recently reported that catheter tip dislocation decreased the analgesic effect of cISBPB. However, little information is available on how far the inserted cISBPB catheter migrated after surgery. In this study, we examined the amount of movement of the inserted catheter after surgery.

The study population included all patients who underwent shoulder surgery and cISBPB by the same anesthesiologist at Saiseikai Niigata Hospital from June 1, 2017 to December 31, 2017. The Ethics Review Board of Saiseikai Niigata Hospital approved this study (registration number: E17–12), and all enrolled patients provided written informed consent. Exclusion criteria were contraindications to continuous interscalene block, body mass index ≥ 30 kg/m\(^2\), and American Society of Anesthesiologists physical status ≥ 3.

Preoperatively, the cISBPB catheter (Perifix\textsuperscript{®} Soft Tip Catheter, B. Braun, Germany) was inserted between the C5 and C6 nerve roots using a posterior in-plane ultrasound-guided approach. Subsequently, agitated saline (0.5 ml of air and 3 ml of saline) was injected through the catheter to identify the catheter position by the hyperechoic flush from the proximal catheter pore in the interscalene space (Fig. 1A), and the images were stored in the internal hard disk of the ultrasound device. The inserted length of the catheter at the skin was recorded, and the catheter was sealed using 2-octyl cyanoacrylate (Aron Alpha\textsuperscript{®} A, Daiichi Sankyo, Japan) and draped using sterile transparent tape (3M Tegaderm\textsuperscript{TM} Film, 3M Health Care, USA). On postoperative day 1 in the ward, the catheter position was identified by hyperechoic flush using the same method, and the dislocation distance from the preoperative proximal catheter pore position was measured by comparison with the images stored on the hard disk (Fig. 1B). When measuring the distance, the preoperative proximal catheter pore position was set in reference to the surrounding anatomical structures, such as the anterior scalene muscle. Movement of the catheter toward the skin was expressed as a positive direction and the opposite direction as a negative direction. The dislocation rate and distance of catheter tip movement were the main outcome parameters. Dislocation was defined as a shallower catheter position than in the initial placement. The correlations between the distance of catheter tip dislo-
cotton and basic patient information, such as age, height, weight, and catheter insertion length, were also analyzed using the Spearman rank correlation coefficient. Values are presented as median (Q1, Q3). P values were two-sided, and statistical significance was defined as P < 0.05.

A total of 27 patients were included in the study, and no patients were excluded. The median age, height, weight, and catheter insertion length were 59 (38.5, 72) yr, 167 (160, 170.5) cm, 70.6 (62.1, 77.7) kg, and 70 (67.5, 80) mm, respectively.

The catheter insertion length did not change after surgery in all cases. Catheter tip dislocation was observed in 22 of 27 cases (81.5%), and the catheter tip was shallower by 11 (3.5, 20.5) mm. Only the insertion length was negatively correlated with the distance of catheter tip dislocation (r = –0.66, 95% CI [–0.84, –0.37], P < 0.001) (Fig. 1C).

We observed that catheter tip dislocation occurred frequently, and the mean dislocation distance was approximately 1 cm. We also found a negative correlation between the distance of catheter tip dislocation and catheter insertion length. From the results of our research, it is expected that a catheter will be more likely to stay in proper position if it is inserted approximately 1 cm deeper than the customary catheter insertion position to secure a margin for catheter movement. However, this could also lead to over-insertion of the catheter, which may increase the risk of complications or even dislodge the catheter tip from the interscalene space. It is safer to perform the above procedure while visualizing the catheter tip using ultrasound to avoid straying. We included even the slightest catheter movement as dislocation, which may be due to the more sensitive assessment method in our study. However, we do not want to emphasize the measurement size itself, but to convey the fact that catheters can easily move inside the body even if the insertion length remains the same.

The main limitation of this study was the lack of standardization of various factors that may be associated with catheter dislocation, such as surgical procedures or patient rest levels, since shoulder and neck movements during and after surgery are considered to be related to catheter tip dislocation. The method of measuring the dislocation distance was also a limitation. Since the ultrasound images of the interscalene region were different before and after surgery, there is no guarantee that the pre- and postoperative comparisons were made accurately. In addition, the method may not accurately reflect dislocation because it is an indirect assessment that measures the hyperechoic region.

In conclusion, we must consider that catheter tip movement easily occurs and is approximately 1 cm in cISBPB. This study suggests that a longer insertion length may provide superior analgesia.

**Funding**

None.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

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**Fig. 1.** Representative ultrasound images of posterior approached-continuous interscalene brachial plexus block at the catheter insertion day and the day after the catheter insertion. (A) The catheter was placed between the C5 and C6 nerve roots and beyond the interscalene space. (B) The catheter was retracted 2.3 cm from the initially placed position setting as A. The position of A in this figure was determined using the anterior scalene muscle as a guide. (C) There was a negative correlation between catheter insertion length and distance of dislocation (r = –0.66, 95% CI [–0.84, –0.37], P < 0.001). White arrow: most proximal port of the catheter available, identified by the hyperechoic flush induced by air, White triangle: catheter visible by ultrasound. ASM: anterior scalene muscle, MSM: middle scalene muscle, LA: local anesthetics.
Author Contributions

Tatsuya Abe (Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Validation; Visualization; Writing – original draft; Writing – review & editing)
Takashi Fujiwara (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision)
Yoshinori Kamiya (Software; Supervision; Visualization; Writing – review & editing)

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References


https://doi.org/10.4097/kja.21227
Acute pulmonary thromboembolism (PTE) is a known complication in patients with respiratory symptoms of coronavirus disease 2019 (COVID-19) [1]. However, acute PTE is rarely reported as a late sequela in asymptomatic or minimally symptomatic COVID-19 [1–3]. We herein present, with consent for publication, a patient with asymptomatic nasopharyngeal reverse transcriptase–polymerase chain reaction (RT-PCR) swab-positive COVID-19 who developed massive acute PTE during the convalescent phase, nearly 4 weeks after two consecutive negative nasal swab results.

A 41-year-old man (weight: 99 kg, height: 177 cm), was diagnosed with asymptomatic COVID-19 disease based on a positive nasopharyngeal SARS-CoV-2 RT-PCR and household contact with a proven COVID-19 case. He had no prior comorbidities, except for deep vein thrombosis induced by lower limb cellulitis 5 years earlier, for which he received anticoagulation therapy for 6 months and had complete recovery. The COVID-19 was managed on home isolation for 16 days until two consecutive nasal swab tests, performed on day 11 and day 15 of the disease, were negative. During this period, he remained ambulatory and received low-dose enoxaparin prophylaxis for 4 weeks. Nearly 42 days following the disease onset, he presented with dyspnea, hypoxemia (room-air oxygen saturation of 91%), and hypotension. Serum D-dimer (> 35,200 ng/ml), C-reactive protein (94.8 mg/L), and troponin-T (1.196 µg/L) levels were elevated. A repeat RT-PCR swab test result was negative. Transthoracic echocardiography showed a large freely mobile right atrial thrombus measuring 5 cm × 0.8 cm attached to the posteroinferior wall, normal left ventricle, dilated right ventricle, severe pulmonary arterial hypertension (systolic pressure 60 mmHg), and moderate tricuspid regurgitation. CT chest images did not show pulmonary consolidation. CT pulmonary angiogram showed extensive right and left pulmonary artery thrombosis and an enlarged right atrium and right ventricle with filling defects. In the first 24 hours, he was treated with intravenous fluids, inotropes, and tissue plasminogen activator, resulting in an improved blood pressure of 110/75 mmHg, heart rate of 76 beats/min, and oxygen saturation of 96% on 2 L/min nasal oxygen. Subsequently, therapeutic-dose subcutaneous enoxaparin was initiated, and transesophageal echocardiography (TEE) was performed to delineate the extent of cardiac thrombosis. 2D and 3D TEE showed a large right atrial thrombus attached to the Chiari network, a stagnated thrombus measuring 1.1 cm × 0.3 cm crossing a patent foramen ovale, thrombosis of both main pulmonary artery branches, right ventricular dilatation with mild dysfunction, and minimal tricuspid regurgitation (Fig. 1). Later, due to significant hemodynamic instability, an emergency pulmonary thrombectomy under cardiopulmonary bypass was performed. Immediate post-bypass TEE showed complete resolution of pulmonary arterial thrombosis; however, severe right ventricular dysfunction was present. Nonetheless, he was weaned from mechanical ventilation the next day and inotropes after...
3 days. Follow-up echocardiography a week later showed no residual thrombus and normal right ventricular function.

While thromboembolic complications occur with an incidence as high as 20% to 30% in patients with severe COVID-19 [1], only a few reports have described such complications following recovery from mild COVID-19 [1,2]. A single-center report of 163 patients without post-discharge thromboprophylaxis suggested a 2.5% cumulative incidence of thrombosis at 30 days following discharge, including segmental pulmonary embolism, intracardiac thrombus, thrombosed arteriovenous fistula, and ischemic stroke [4]. Tu et al. [5] recently reported 10 cases of acute ischemic stroke in adults aged ≤ 50 years in the convalescent phase of asymptomatic COVID-19. The median (Q1, Q3) time from a positive serological test result to acute ischemic stroke was 54.5 (0, 130) days. However, none of these patients had received thromboprophylaxis. Thus, the present case is unique, as the patient developed massive acute pulmonary embolism nearly 42 days post-asymptomatic COVID-19 despite thromboprophylaxis.

Further, this case highlights the possibility of prolonged COVID-19-associated coagulopathy (CAC) following asymptomatic SARS-CoV-2 infection resulting in massive cardiopulmonary thrombosis in the convalescent phase. Pow et al. [2] reported a similar case of submassive pulmonary embolism during the convalescent phase in a patient with minimally symptomatic SARS-CoV-2 infection. However, as their patient had a positive nasal swab result on readmission, it raised the possibility of reinfection resulting in a hypercoagulable state instead of prolonged CAC as a cause of submassive pulmonary embolism. Probable mechanisms

Fig. 1. (A) 2D transesophageal echocardiogram images show a large right atrial thrombus (T) in 4-chamber view and (B) right ventricular inflow-outflow view. (C) 3D transesophageal echocardiogram image shows thrombus-in-transit through a patent foramen ovale (P). (D) CT pulmonary angiography shows bilateral pulmonary thrombi.

https://doi.org/10.4097/kja.21199
of CAC and thrombosis in post-acute COVID-19 syndrome include dysregulated renin-angiotensin system activity, endothelial dysfunction, cytokine-induced inflammation, complement and platelet activation, platelet-leukocyte interaction, neutrophilic extracellular traps, lupus anticoagulant, and up-regulation of tissue factor, thrombin, and fibrin with down-regulation of fibrinolytic and anticoagulant mechanisms [1,2,4]. The risk of thrombotic complications in the post-acute COVID-19 phase is probably linked to the duration and severity of a hyperinflammatory state, although how long this persists is unknown [4].

Given the increase in thrombotic complications in post-acute COVID-19, Nalbandian et al. [4] argued that extended post-hospital follow-up (up to 6 weeks) and prolonged primary thromboprophylaxis (up to 45 days) in those managed as outpatients may have a more favorable risk–benefit ratio. However, individual patient-level considerations for risk versus benefit should dictate recommendations at this time. Elevated D-dimer levels, in addition to comorbidities such as cancer and immobility, may help to stratify patients at the highest risk of post-acute thrombosis [4]. Notably, increased D-dimer levels (> 500 ng/ml) were observed in 25.3% of patients up to 4 months post-SARS-CoV-2 infection [3]. Thus, elevated D-dimer levels and history of deep vein thrombosis (even though not associated with hypercoagulable disorders) might have placed our patient at high risk of thrombotic complications despite thromboprophylaxis and ambulation. Furthermore, as optimal therapy is not defined for COVID-19-associated thrombosis, thrombolytic therapy might have resulted in an unfavorable outcome in our patient.

In conclusion, we highlight the possibility of late-onset acute COVID-19-associated thrombosis even in asymptomatic infections, the lack of an established dose and duration of thromboprophylaxis, and the risk of failure of thrombolytic therapy. Close patient follow-up is warranted in the convalescent phase of COVID-19.

**Funding**

None.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Author Contributions**

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Amit Jain (Conceptualization; Writing – review & editing)

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**References**

Clavicle fixation is becoming more common but only a few comparative studies have been conducted to determine the optimal approach in regional anesthesia as the sole modality for such surgery. Combined interscalene and intermediate cervical plexus block seems to be the most effective technique [1]. However, this approach can be associated with undesirable effects and may be contraindicated in patients with impaired pulmonary function [2].

The wide awake local anesthesia with no tourniquet (WALANT) technique was recently reported as an alternative landmark-based technique for clavicle fractures [3]. This technique involves injecting diluted and buffered local anesthesia with epinephrine under the clavicular periosteum. We describe the use of ultrasound guidance to perform this technique in two patients undergoing clavicle surgery. This study was approved by the local Institutional Review Board committee (approval number: 2020-09). Written informed consent was obtained from the patients.

A 17-year-old patient was admitted for a displaced segmental fracture of the midshaft clavicle. The patient was placed in a semi-fowler position with the head turned away from the operative side. The anesthetic solution prepared was a mixture of 0.5% lidocaine containing 0.05% bupivacaine, epinephrine 1/200000, and 8.4% sodium bicarbonate (1 ml per 10 ml of lidocaine). We used a linear ultrasound probe (13-6 MHz, SonoSite Edge II, USA) to scan above and below the clavicle to identify relevant nearby structures particularly the pleura, brachial plexus, and subclavian vessels. After subcutaneous injection of 10 ml over the incision line, ultrasound-guided WALANT was performed by administering 40 ml of the prepared solution at four intervals along the clavicle. The probe was placed perpendicular to the long axis of the clavicle to view the bone in cross section (Fig. 1A). A conventional needle (21 gauge × 38 mm) was inserted vertically out-of-plane until the needle tip contacted the clavicle. Local anesthetic was injected, then the needle was withdrawn to the skin level and redirected cranially and caudally until bone contact to anesthetize the borders of the clavicle. Ultrasound guidance allowed visualization of adequate spread around the cortical line of the clavicle. Thickening of the hyperechoic and thin cortical line with subsequent lower echogenicity and fuzzy edges was also observed (Fig. 1B), confirming spread of the anesthetic solution under the periosteum (Supplemental Video 1). Additionally, 5 ml of anesthetic mixture was injected into the fracture site under ultrasound guidance using an in-plane technique. Surgical incision was begun after 30 min to allow maximal vasoconstriction and optimal sensory anesthesia of the clavicular area. There was no motor or sensory block of the upper limb, indicating ab-
sence of spread of local anesthetic solution to the brachial plexus. The 70 min procedure was performed successfully without sedation, and a clavicle plate was fixed using screws. Stability of the fixation was evaluated using active shoulder movements. No surgical drain was required. Intravenous acetaminophen (1 g) and ketoprofen (100 mg) were administered. No supplemental analgesics were used, and the patient was discharged after 24 h.

The second case involved a 45-year-old man, who had undergone surgery for an acromioclavicular dislocation treated with tension band wiring and a medial malleolus fracture fixed using Kirschner wires (K-wires). The patient was scheduled for hardware removal. After anesthetic skin infiltration, we performed ultrasound-guided WALANT at the lateral portion of the clavicle and the acromioclavicular junction using the previously described technique (Fig. 1C). We administered a total of 50 ml of local anesthetic solution prepared as described above, including 10 ml injected into the medial malleolus. The same ultrasonographic image was observed after subperiosteal injection, with visualization of the spread of local anesthetic around the entry points of the K-wires (Fig. 1D). The surgery lasted 25 min with no additional analgesic requirement. No adverse effects were observed. The patient reported no pain in the immediate postoperative period, required no rescue analgesia and was discharged on the same day with oral medication.

Although the benefits of ultrasound guidance in WALANT have been reported for hand surgery [4], our report is the first to examine its clinical utility for clavicle procedures. Ahmad et al. [3] expanded the use of WALANT to clavicle surgery and reported 16 patients who successfully underwent clavicle fixation. However, two patients with displaced segmental fractures experienced mild pain during fixation. Anesthesia was then completed by intraoperatively injecting a supplemental WALANT solution. No complications were observed in this first case series, suggesting that this approach may be an effective alternative. However, special precautions must be taken when injecting blindly near the lung, brachial plexus, and subclavian vessels. This encouraged us to perform this technique under ultrasound guidance. Advantages of this method include the ability to visualize the correct spread of local anesthetic around the clavicle, and to avoid inadvertent puncture of adjacent structures. Remarkably, subperiosteal diffusion results in a typical thickening and echotexture modification of the cortical line. Ultrasound guidance also allows the deposition of local anesthetic around the fixation devices and into the fracture site, thus avoiding supplementary intraoperative injections.

In addition to its technical simplicity, WALANT might reduce the risk of nerve damage and phrenic nerve palsy associated with regional techniques commonly used for awake clavicle repair [2].
Although WALANT is performed anatomically distant from the phrenic nerve, theoretically precluding its involvement, we did not assess diaphragmatic function by ultrasound to validate this. Moreover, WALANT avoids motor blockade of the upper limb, allowing the patient to dress independently right after surgery, and making it suitable for outpatient surgery. Active patient movements also assist the surgeon in assessing fixation stability. However, there are some concerns including delayed onset of blockade and patient discomfort due to prolonged surgery [3].

We have presented two cases describing the advantages of ultrasound guidance in WALANT for clavicle surgery, with a novel ultrasonographic image of subperiosteal injection. Effective postoperative analgesia and the absence of upper limb motor blockade facilitate early recovery. This alternative could constitute a diaphragm sparing option in patients with respiratory impairment, but also in more common cases. Further investigation is required to establish the efficiency and safety of this novel technique.

**Funding**

None.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Author Contributions**

Khalid Azizi (Conceptualization; Resources; Writing – original draft; Writing – review & editing)
Sabah Benhamza (Supervision; Validation; Visualization; Writing – review & editing)
Youssef Motiaa (Supervision; Validation; Visualization; Writing – review & editing)

**Supplementary Material**

Supplemental Video 1. Ultrasonographic video of the subperiosteal spread of local anesthetic after out-of-plane WALANT injection. Note the thickening and echotexture modifications of the clavicular cortical line.

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**References**


https://doi.org/10.4097/kja.21282
Gupta et al. [1] recently conducted an interesting meta-analysis on the comparative characteristics of video laryngoscopy (VL) compared to direct laryngoscopy (DL) for nasotracheal intubation (NTI) in oromaxillofacial surgeries. This well-conducted meta-analysis of randomized controlled trials included data from 10 studies and showed that VL had significant advantages in terms of time to intubation (TTI) (mean difference, −9.04 s) and first-attempt success rate (SR) (relative risk [RR] 1.10) and required fewer maneuvers to facilitate intubation (RR 0.22). No differences were detected between VL and DL in terms of the overall intubation SR or incidence of nasal bleeding. The authors concluded that VL should be considered over DL for NTI in oromaxillofacial surgeries.

In order to assess the robustness of these findings, a trial sequential analysis (TSA) of the investigated outcomes is warranted before drawing strong conclusions in support of VL. Conducting a TSA helps to reduce the risks of type I statistical errors by providing evidence of the required information size (sample of patients needed) for the reported outcomes. We used TSA Software (Copenhagen Trial Unit’s TSA Software®, Denmark) to perform the analysis. The information size was computed assuming an alpha risk of 5% with a power of 80%. We used a random-effects model and for the estimated effects on the investigated outcomes, we used the mean difference reported by Gupta et al. [1] for the continuous outcomes and RR reduction for dichotomous outcomes. Further details on TSAs and their interpretation are available elsewhere [2,3].

We conducted three TSAs in total to investigate the robustness of the study’s finding that VL is superior to DL for NTI in terms of TTI and first-attempt SR and to compare the number of maneuvers required for intubation. The TSAs showed that the required information size (or sample size needed) was achieved for all three outcomes, with a ratio of patients recruited/patients needed of 597/202 for TTI (Fig. 1), 467/263 for first-attempt SR, and 537/383 for the number of maneuvers required.

Importantly, all the TSAs conducted confirmed that the findings of Gupta et al. [1] were robust, as the Z-curve of effect crossed the adjusted significance thresholds for all the analyses.

In summary, while the authors conducted a scrupulous meta-analysis, performing a TSA is necessary to confirm the robustness of the investigated outcomes and to provide further support for the use of VL over DL for NTI in oromaxillofacial surgeries.
Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Luigi La Via (Conceptualization; Methodology; Project administration; Supervision; Writing – original draft)
Simone Messina (Data curation; Formal analysis; Methodology)
Federica Merola (Data curation; Formal analysis; Software)
Filippo Sanfilippo (Conceptualization; Validation; Writing – review & editing)
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Fig. 1. Trial sequential analysis (TSA) on time to intubation (TTI). RE: random effect, MD: mean difference, VL: video laryngoscopy, DL: direct laryngoscopy.

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References

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⁶Lee S and Lee DK. What is the proper way to apply the multiple comparison test? Korean J Anesthesiol 2018; 71: 353-60.
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The introduction should address the purpose of the article concisely and include background reports that are relevant to the purpose of the paper.
④ Materials and Methods
- The materials and methods section should include sufficient details of the design, subjects, and methods of the article in order, as well as the data analysis methods and control of bias in the study. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others.
- When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the IRB for the study and the IRB approval number needs to be provided. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by Institutional Board for the Care and Use of Laboratory Animals. “American Society of Anesthesiologists physical status classification” should not be abbreviated. As a rule, subsection titles are not recommended.
- Clearly describe the selection of observational or experimental participants. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors
should justify why, except in obvious cases (e.g., prostate cancer). For additional information, please visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/.

- Reports of randomized trials must conform to the revised CONSORT guidelines and should be submitted with the CONSORT flow diagram. The CONSORT checklist should be submitted as a separate file along with the manuscript. The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org or EQUATOR Network (https://www.equator-network.org/home/)

- Units
  Laboratory information should be reported in International System of Units [SI]. Please refer to A Guide for Biological and Medical Editors and Authors, 6th Edn. Baron DN and Clarke HM, ed. (2008), CRC Press. or visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/

- Exceptions
  A. The unit for volume is “L”, others in “dl, ml, μl”.
  B. The units for pressure are mmHg or cmH₂O.
  C. Use Celsius for temperature
  D. Units for concentration are M, mM, μM.
  E. When more than 2 items are presented, diagonal slashes are acceptable for simple units. Negative exponents should not be used.
  F. Leave 1 space between number and units.
  Exception) 5%, 36°C

- Drug Names and Equipment
  Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide ® or ™ as a superscript and manufacturer’s name, and country.

- Ions
  Ex) Na⁺ [O], Mg²⁺ [O], Mg⁺³ [X], Mg⁺² [X]

- Statistics
  Statistical methods must be described with enough detail so that readers can reproduce the same results if the original data available. The KJA strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. A sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint.

☺ Discussion
  The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat the results in detail or other information that is given in the Introduction or the Results section. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the Discussion section.

☺ References

  - References should be obviously related to documents and should not be exceed 50. For exceeding the number of references, it should be negotiated with the Editorial Board. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide footnotes in the body text section. All of the references should be stated in English, including author, title, name of journal, etc.
  - If necessary, the editorial board may request original documents of the references.
  - Six authors can be listed. If more than 6 authors are listed, only list 6 names with ‘et al.’
  - Provide the start and final page numbers of the cited reference.
  - Abstracts of conferences are not allowed to be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.
  - Description format
    A. Regular journal
    Author name. Title of journal Name of journal published
of line drawings should be at least 1,200 dpi. Number figures as “Fig. (Arabic numeral)” in the order of their citation. (ex. Fig. 1).

② Photographs should be submitted individually. If Figure 1 is divided into A, B, C and D, do not combine it into 1, but submit each of them separately. Authors should submit line drawings in black and white.

③ In horizontal and vertical legends, the letter of the first English word should be capitalized.

④ Connections between numbers should be denoted by “- “, not “~ “. Do not space the numbers (ex. 2–4).

⑤ Figures (line drawings) should be clearly printed in black and white.

⑥ Figures should be explained briefly in the footnotes. The format is the same as the table format.

⑦ An individual should not be recognizable in the photographs or X-ray films unless written consent of the subject has been obtained and is provided at the time of submission.

⑧ Pathological samples should be pictured with a measuring stick.

⑨ Figures (line drawings) should be clearly printed in black and white.

⑩ Figures should be explained briefly in the footnotes. The format is the same as the table format.

(4) Other submission elements (Video submission)
The KJA publishes supplemental video (movie) clip(s) that will be available online. Not only recording of the abstract, text, audio or video files, but also data files should be added here.

Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and be discussed in the text. Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) in the video clips. However, all identifying information, including patient name and/or ID number, hospital name, and date of the procedure, should be removed.

Video clips should contain succinct teaching points that must be supported by the current literature or standard reference texts, preferably those most accessible to the general reader. The adequacy of the teaching points will be evaluated during the review process and finally confirmed by the editorial board at the end of the review process.

Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.

① The video clip(s) should have simple file names (e.g., Video 1***, Video 2****) and include the appropriate extension (e.g., .mov, .mpg).

② The maximum number of video clips is 20.

③ The video clip(s) should be playable on both Windows and MAC computers. The video clip(s) should be tested for play-back before submission, preferably on computers not used for their creation, to check for any compatibility issues.

④ Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.

⑤ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

2) Systematic review and meta-analysis
Systematic reviews are systematic, critical assessments of literature and data sources in order to answer a specific question, and/or includes a statistical technique leading to a quantitative summary of results and examining sources of differences in results among studies, if any. The subtitle should include the phrase “A systematic review” and/or “A Meta-analysis.”

Organization of systematic review and meta-analysis: Same as clinical and experimental studies, except,

- All systematic reviews and meta-analyses should be registered at an appropriate online public registry (eg, PROSPERO; http://www.crd.york.ac.uk/PROSPERO/), and registration information should be included with the submission.
- Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/). Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.
- No limitation the number of the references.

3) Case Reports
A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or
population, that is so unusual that a clinical trial is not feasible.

Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.

(1) Title page: Same as clinical and experimental studies.

(2) Manuscript

① Title and Running title.
② Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH [http://www.ncbi.nlm.nih.gov/mesh] and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.
③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.
④ Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.
⑤ Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.
⑥ References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board. A figure or a table may be used. A maximum of five authors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.
⑦ Tables and figures: Proportional to clinical and experimental studies.

4) Reviews

Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts equal to or less than 250 words in English. Figures and tables should be provided in English. References should be obviously related to documents and should not be exceed 100. For exceeding the number of references, it should be negotiated with the Editorial Board. Body text should not exceed 30 A4 pages, and the number of figures and tables should be equal to or less than 6.

5) Letters to the Editor

Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included. Letters to the editor of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Letters to the Editor cover individual articles not described by any of the above categories. The short manuscripts with a constructive note on the Journal or the anesthesiology at large are welcome.

Cover pages should be formatted as those of clinical research papers. The body text should not exceed 1,000 words and should have no more than 5 references. For exceeding the number of references, it should be negotiated with the Editorial Board. A figure or a table may be used. A maximum of five authors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.

6) Statistical Round

A Statistical Round is a narrative review of the application of contemporary quantitative sciences to issues of concern to anesthesiology researchers. A Statistical Round involves a focused discussion on one or more unique or interesting statistical analysis methods that has previously been published in this journal or expresses the general policies or opinions of the Statistical Round Board. They are solicited by the Statistical Round Board and reviewed by the Statistical Editor. There are no word limits to or rules regarding the structure of a Statistical Round. They should have an unstructured abstract of no more than 250 words in English. All articles in a Statistical Round will be published in English and translated into Korean for the convenience of Korean readers. The Korean version of the Statistical Round will be published only on the Web page of the Journal [https://ekja.org]. The inclusion of sample datasets as Web (Supplemental) content is encouraged.

8. Recently revised instructions for authors are applied from February 2021 submissions.