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Anesthetic considerations for urologic surgeries

 비뇨기 수술을 위한 마취 고려사항

Chang-Hoon Koo¹, Jung-Hee Ryu¹,²

Department of Anesthesiology and Pain Medicine, ¹Seoul National University Bundang Hospital, Seongnam, ²Seoul National University College of Medicine, Seoul, Korea

비뇨기 수술은 다양한 규모의 병원에서 광범위하게 실시되고 있으며, 노인 인구의 증가로 인해 그 증례가 계속 증가하고 있다. 수술 공간(surgical space)이 좁고 제한적이어서 마취과 의사가 관찰하기 어려우며, 대부분의 비뇨기 수술이 주술기 합병증 발생 위험이 높은 노인 인구에서 행해지고 있다는 점에서 환자 관리의 어려움이 크다. 따라서, 수술 중 마취를 최적화하기 위한 포괄적인 이해와 접근법이 필요하다. 이에 저자들은 비뇨기 수술을 위한 마취와 관련된 문제들에 대한 체계적인 문헌 고찰을 통해 마취 시 고려해야 할 사항들을 정리하였다.

Keywords: General anesthesia; Geriatrics; Perioperative care; Postoperative complication; Spinal anesthesia; Urologic surgery.
Management of perioperative volume therapy – monitoring and pitfalls

주술기 혈액량 관리 요법(volume therapy) – 주요 관찰 내용 및 주의점

Michael Sander*, Emmanuel Schneck†, Marit Habicher

Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Giessen, UKGM, Justus-Liebig University Giessen, Giessen, Germany

Keywords: Cardiac output monitoring; Colloids; Crystalloid solutions; Hemodynamic monitoring; Hypotension; Volume therapy.
Tips for troublesome sample-size calculation

연구대상자 수 계산을 위한 조언

Junyong In¹, Hyun Kang², Jong Hae Kim³, Tae Kyun Kim⁴, Eun Jin Ahn⁵, Dong Kyu Lee⁶, Sangseok Lee⁷, Jae Hong Park⁸

Department of Anesthesiology and Pain Medicine, ¹Dongguk University Ilsan Hospital, Goyang, ²Chung-Ang University College of Medicine, Seoul, ³Daegu Catholic University School of Medicine, Daegu, ⁴Yangsan Hospital, Pusan National University School of Medicine, Busan, ⁵Inje University Seoul Paik Hospital, Inje University College of Medicine, ⁶Guro Hospital, Korea University College of Medicine, ⁷Sanggye Paik Hospital, Inje University College of Medicine, Seoul, ⁸Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

정확하게 설정된 연구대상자 수는 과학적이고 설득력 있는 연구를 위한 중요한 요소 중 하나이다. 재정적 혹은 의학적 측면에서 과도한 부담을 야기하지 않으면서도, 연구자가 관심을 가지는 현상에서 임상적으로 유의한 차이와 적절한 검정력을 모두 보장할 수 있는 연구대상자 수는 언제나 관심의 대상일 수밖에 없다.

본 원고에서는 연구대상자 수 계산에 필수적인 요소들을 하나씩 살펴보았다. 연구의 주 관심사이자 연구대상자 수 계산의 바탕이 되는 일차 유효성 평가변수, 평가변수의 분석에 사용된 통계량, 제1형 오류와 검정력, 그리고 효과크기와 그 근거에 대해 살펴보았다. 또한, 연구과정에서 필연적으로 발생하는 연구대상자의 탈락률을 고려하여 최종적인 연구대상자 수를 계산하는 방법도 포함하였다. 마지막으로 기존에 발표된 논문들에서 적절하게 기술된 예와 잘못 기술된 예를 설명하고 함께 제시하였다.

Keywords: Biostatistics; Effect size; Independent t-test; Power; P value; Sample size.
배경: 제왕절개술 후 통증조절을 위한 초음파 유도하 양측 요방형근차단 대 척수강 내 모르핀의 효과 비교: 무작위 배정 대조 임상시험

Eman Ramadan Salama
Department of Anesthesia and Surgical Intensive Care, Faculty of Medicine, Tanta University, Tanta, Egypt

배경: 제왕절개(cesarean section, CS) 후의 적절한 통증 관리는 신생아를 돌보는 산모 및 혈전색전증과 만성 복통 및 골반통을 피하기 위한 조기 보행에 중요한 요소이다. 이 무작위 배정 대조 임상시험은 제왕절개 후 진통을 위한 요방형근차단(quadratus lumborum block, QLB)과 척수강 내 모르핀(intrathecal morphine, ITM)의 유효성을 비교하였다.

방법: 선택적 제왕절개가 예정된 임신 37주 이상의 여성 90명이 대상이며, 모든 환자는 척추마취와 수술 후 QLB를 받았다. 환자들은 (마취: 식염수 0.1 ml, QLB: 식염수 24 ml), ITM 군(마취: 모르핀 0.1 mg, QLB: 식염수 24 ml) 또는 QLB 군(마취: 모르핀 0.1 ml, QLB: 0.375% 로피바카린 24 ml)에 무작위 배정되었다. 안정 시 및 운동 중 종합 진통 점수(Integrated Analgesia Score, IAS) 및 수치 숫자평가척도(Numerical Rating Scale, NRS) 점수, 첫 48시간의 모르핀 요구량, 첫 모르핀 투여까지의 시간, 첫 보행까지의 시간, 환자 만족도 및 모르핀 관련 부작용을 기록하였다.

결과: 안정 시 및 운동 중 IAS 및 NRS 점수는 대조군에서보다 QLB와 ITM에서 유의하게 더 낮았다. 또한, 안정 시 및 운동 중 IAS 및 NRS 점수는 ITM에서보다 QLB에서 더 낮았다. 첫 번째 모르핀 투여까지의 시간은 ITM 및 대조군에서보다 QLB에서 유의하게 더 길었다. 또한, 첫 48시간의 모르핀 요구량은 ITM 및 대조군에서보다 QLB에서 유의하게 낮았다. 모르핀 관련 부작용 발생률은 QLB 및 대조군에서보다 ITM에서 유의하게 높았다.

결론: QLB와 ITM은 CS 제왕절개 이후 효과적인 진통 요법이다. 그러나 QLB가 더 우수하게 지속적인 진통작용을 제공했으며 수술 후 총 모르핀 사용량을 감소시켰다.

Keywords: Analgesia; Cesarean section; Morphine; Quadratus lumborum; Spinal.
Long-term mortality of patients discharged from the hospital after successful critical care in the ICU in Korea: a retrospective observational study in a single tertiary care teaching hospital

Se Hee Na¹², Cheung Soo Shin¹², Gwan Ho Kim¹, Jae Hoon Kim¹, Jong Seok Lee¹²

¹Department of Anesthesiology and Pain Medicine, ²Anesthesia and Pain Research Institute, Yonsei University College of Medicine, Seoul, Korea

배경: 중환자실(intensive care unit, ICU)에서의 집중치료를 받고 질병이 호전되어 퇴원한 한국 환자의 장기적 결과를 평가하고자 본 연구를 수행하였다. 본 연구의 목표는 ICU에서 치료를 받고 퇴원한 환자의 장기적 사망률을 평가하고 사망의 예측 인자를 확인하는 것이다.

방법: 2006년부터 2011년 사이에 집중치료 후 퇴원한 성인 환자 3,679명을 대상으로, 1년 사망률(일차 결과 척도)을 조사하였다. 1년 사망률에 영향을 미친 독립 인자를 확인하기 위한 다변량 분석에서 성별, 연령, 질병의 중증도(APACHE II 점수), 기계 환기, 악성종양, 재입원, 입원 형태(응급, 계획 수술 및 내과적 원인), 진단 유형(외상 및 비외상) 등 다양한 인자가 포함되었다.

결과: 집중치료 후 병원에서 퇴원한 환자에서 1년 사망률은 13.4%였다. 1년 사망률과 관련된 위험인자에는 연령(위험비: 1.03; 95% CI, 1.02-1.04; P < 0.001), APACHE II 점수(1.03; 1.01-1.04; P < 0.001), 기계 환기(1.96; 1.60-2.41; P < 0.001), 악성종양(2.31; 1.82-2.94; P < 0.001), 재입원(1.65; 1.31-2.07; P < 0.001), 응급 수술(1.66; 1.18-2.34; P = 0.003), 내과적 원인(4.66; 3.68-5.91; P < 0.001), 비외상성 진단(6.23; 1.58-25.08; P = 0.01)이 포함되었다.

결론: 1년 사망률은 13.4%였다. 고령, 높은 APACHE II 점수, 기계 환기, 악성종양, 재입원, 응급 수술, 내과적 원인으로 인한 ICU 입원, 내과적 진단이 1년 사망률과 관련이 있었다.

Keywords: Critical care outcomes; Intensive care unit; Long-term outcomes; Mortality; Risk factors; Survival analysis.
Neuromuscular blockade reversal with sugammadex versus pyridostigmine/glycopyrrolate in laparoscopic cholecystectomy: a randomized trial of effects on postoperative gastrointestinal motility

Jihyun An, Heeyun Noh, Eunju Kim, Jihyang Lee, Kyeongyoon Woo, Hyunkyum Kim

Department of Anesthesiology and Pain Medicine, Daegu Fatima Hospital, Daegu, Korea

Keywords: Cholinergic antagonists; Defecation; Flatulence; Gastrointestinal motility; Glycopyrrolate; Pyridostigmine bromide; Sugammadex.
Efficacy of trospium for prevention of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study

Vinit Kumar Srivastava¹, Sanjay Agrawal², Sweta Anil Deshmukh¹, Febin Noushad¹, Saima Khan¹, Raj Kumar³

Department of Anesthesiology, ¹Apollo Hospitals Bilaspur, Chhattisgarh, ²All India Institute of Medical Sciences, Rishikesh, Uttarakhand, ³Department of Neurosurgery, Apollo Hospitals Bilaspur, Chhattisgarh, India

배경: 도뇨관 관련 방광 불편(catheter-related bladder discomfort, CRBD)은 수술기에 방광 도뇨관 삽입을 받은 환자가 마취 회복 후 자주 호소하는 증상이다. 과활동성 방광(overactive bladder, OAB)과 CRBD는 유사한 증상을 보인다. 따라서 OAB의 관리에 사용되는 약물인 염화트로스피움(trospium chloride)은 CRBD의 증상 완화에 도움을 줄 수 있다. 이 연구에서는 수술 후 기간에 CRBD에 대한 경구용 트로스피움의 유효성을 평가하였다.

방법: 척추 수술이 계획되어 있으며 방광 도뇨관 삽입을 요하는 64명의 남성 및 여성 성인 환자를 각각 32명씩 2개 군으로 무작위로 나누었다. T군의 환자들에게는 서방형 경구 트로스피움 60 mg을 마취 유도 1시간 전에 투여했으며, C군의 환자들에게는 유사한 외관의 위약을 투여했다. 두 군 모두에서 마취 기법은 동일했다. CRBD 중증도는 4점 척도(1=불편 없음, 2=경증, 3=중등증, 4=중증)로 나타났다. T군의 환자들에게는 서방형 경구 트로스피움 60 mg을 마취 유도 1시간 전에 투여했으며, C군의 환자들에게는 유사한 외관의 위약을 투여했다. 두 군 모두에서 마취 기법은 동일했다. CRBD 중증도는 4점 척도(1=불편 없음, 2=경증, 3=중등증, 4=중증)로 나타났다. CRBD 점수는 회복실 도착 시(0 h), 수술 후 1 h, 2 h, 및 6 h에 기록했다. 모든 환자가 수술 후 통증 완화를 위해 펜타닐(fentanyl)을 투여 받았다.

결과: CRBD의 발생률은 0 h (66% vs. 22%, P = 0.001) 및 수술 후 1 h (72% vs. 28%, P = 0.001)에 C군에서 T군 대비 유의하게 더 높았다. 중등도~중증 CRBD의 발생률은 수술 후 2 h에 C군에서 더 높았다 (82% vs. 14%, P = 0.004). 수술 후 펜타닐 요구량에서 유의한 차이는 없었다.

Keywords: Muscarinic antagonists; Muscarinic receptors; Overactive bladder; Postoperative period; Trospium chloride; Urinary catheterization.
Effect of BMS-470539 on lipopolysaccharide-induced neutrophil activation

지질다당류로 유발된 호중구 활성화에 대한 BMS-470539의 영향

Seongheon Lee¹, Wan Ju¹, Tran Duc Tin², Joungmin Kim¹, Jeong Seok Lee³, Cheon Hee Park³, Sang Hyun Kwak¹,²

¹Department of Anesthesiology and Pain Medicine, Chonnam National University Medical School & Hospital, ²Brain Korea 21 Project, Center for Creative Biomedical Scientists at Chonnam National University, ³Department of Anesthesiology and Pain Medicine, Gwangju Christian Hospital, Gwangju, Korea

 배경: Melanocortin 1 수용체에 대한 선택적 작용제인 BMS-470539는 항염증 효과를 가진 것으로 알려져 있다. 본 연구에서는 인간의 호중구를 지질다당류(lipopolysaccharide, LPS)로 자극시킬 때 나타나는 염증반응 및 세포자멸사의 지연에 미치는 BMS-470539의 영향과 신호전달경로를 조사하였다.

방법: 분리한 인간 호중구를 LPS (100 ng/ml)가 있거나 없는 상태에서 여러 농도의 BMS-470539 (1, 10 및 100 \(\mu\)M)와 함께 배양하고, 종양 괴사인자 알파(tumor necrosis factor alpha, TNF-α), 인터루킨(interleukin, IL)-6 및 IL-1β와 같은 전염증성 사이토카인의 발현을 평가하였다. 또한, LPS로 자극시킨 호중구에서 세포외 신호조절 키나아제(extracellular-signal-regulated kinase, ERK)1/2, p38 및 c-Jun N-말단 키나아제(JNK)와 같은 미토겐 활성화 단백질 키나아제(mitogen-activated protein kinase, MAPK)의 발현 및 핵인자 카파 B(NF-κB)의 발현에 대한 BMS-470539의 영향을 효소결합 면역흡착 분석으로 평가하였다. BMS-470539 처리를 하거나 하지 않은 상태에서 호중구를 LPS로 자극시켰을 때 세포자멸사 정도를 형광 활성화 세포 분류(annexin V/프로피듐 아이오다이드) 방법으로 측정하였다.

결과: BMS-470539는 LPS에 의해 유발되는 전염증성 사이토카인의 발현과 MAPK 및 NF-κB의 인산화를 역agini었다. LPS로 자극시킨 호중구에서는 대조군보다 세포자멸사의 발생이 감소하였지만, BMS-470539는 LPS에 의한 세포자멸사의 감소를 유의하게 억제했다.

결론: BMS-470539는 MAPK 경로 또는 NF-κB 경로의 억제를 통해 LPS에 의한 호중구의 염증 반응을 줄여주며, LPS에 의한 호중구 세포자멸사의 지연을 억제할 수도 있다.

Keywords: Apoptosis; BMS-470539; Cytokines; Lipopolysaccharides; Mitogen-activated protein kinases; Neutrophils; NF-kappa B.
Continuous quadratus lumborum block as part of multimodal analgesia after total hip arthroplasty: a case report

Hahyeon Bak\textsuperscript{1,2}, Seunguk Bang\textsuperscript{1,2}, Subin Yoo\textsuperscript{1,2}, Seoyeong Kim\textsuperscript{1,2}, So Yeon Lee\textsuperscript{1,2}

Departments of Anesthesiology and Pain Medicine, \textsuperscript{1}Daejeon St Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, \textsuperscript{2}College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: After total hip arthroplasty, analgesia is usually managed by extradural or local anesthesia. However, quadratus lumborum block (QLB) is a simple and easy method to provide a complete pain relief. Therefore, QLB could be an option for multimodal analgesia after total hip arthroplasty.

Case report: A 83-year-old male underwent total hip arthroplasty and received QLB as part of multimodal analgesia. The patient was given patient-controlled analgesia (PCA) and daily 0.2% ropivacaine 8 ml/h via a percutaneous catheter. The patient's pain score was below 4 during the first 5 days after surgery. Additional analgesics were not required.

Conclusion: QLB can be an option for multimodal analgesia after total hip arthroplasty.
Ultrasound-guided percutaneous intercostal cryoanalgesia for multiple weeks of analgesia following mastectomy: a case series

Rodney A. Gabriel1,2*, John J. Finneran1, Matthew W. Swisher1, Engy T. Said1, Jacklynn F. Sztain1, Bahareh Khatibi1, Anne M. Wallace3, Ava Hosseini1, Andrea M. Trescot4, Brian M. Ilfeld1

Departments of 1Anesthesiology, Division of Regional Anesthesia and Acute Pain, 2Medicine, Division of Biomedical Informatics, 3Surgery, University of California, San Diego, La Jolla, CA, 4Pain and Headache Center, Eagle River, AK, USA

Keywords: Acute pain; Cryoneurolysis; Cryoanalgesia; Mastectomy; Regional anesthesia.

배경: 유방절제술 후 통증은 비교적 오랜 시간 동안 지속되어 상대적으로 지속 시간이 짧은 부위마취를 이용한 통증 조절에는 제한이 있다.

증례: 유방절제술 후 통증 치료를 위해 수술 전 초음파 유도 경피 늑간신경 냉동신경박리는 수술 후 3명의 환자에서 수치 평가 척도(numeric rating scale, NRS)에서의 평균 통증 점수는 수술 당일에 0이었다. 또한, 수술 후 전제기간 동안 추가로 마약성 진통제를 필요로 한 환자는 없었다. 같은 기간에서 통증으로 인한 불면 또는 수면 중 각성은 보고되지 않았다. 이는 과거 연구의 코호트 대비 유의한 향상이었다.

결론: 초음파 유도 경피 냉동진통법은 현재의 다른 방법보다 좀 더 오래 지속되는 유방절제술 후 통증에 효과적인 새로운 진통방법이다. 잠재적 유익성 및 위해성을 입증하고 정량하기 위해서는 적절한 검정력을 갖는 추가적인 무작위 비교 임상시험이 필요하다.

Keywords: Acute pain; Cryoneurolysis; Cryoanalgesia; Mastectomy; Regional anesthesia.
Limited advantage of sugammadex reversal over the traditional neuromuscular reversal technique in terms of postoperative recovery of bowel function

Duk Kyung Kim

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

Sugammadex provides rapid and reliable neuromuscular reversal from any depth of block, and its clinical use is increasing. Although evidence is limited to conclude that the routine use of sugammadex contributes to overall cost reduction, little doubt exists regarding the superiority of sugammadex over neostigmine or pyridostigmine.

Sugammadex, a modified γ-cyclodextrin, acts by forming very tight water-soluble complexes at a ratio of 1:1 with steroidal neuromuscular blocking drugs (rocuronium > vecuronium > pancuronium). Both sugammadex and the sugammadex–rocuronium complex are chemically inert and therefore have no direct effects on the cholinergic receptors. However, traditional reversal technique for neuromuscular blocks using an admixture of anticholinesterase and anticholinergic drugs can pose undesirable gastrointestinal effects, depending on the used drug and dose ratio.

In the April 2020 issue of the Korean Journal of Anesthesiology, An et al. [1] compared postoperative gastrointestinal motility between sugammadex and the combination of pyridostigmine and glycopyrrolate in patients undergoing laparoscopic cholecystectomy. This randomized controlled study revealed that the use of sugammadex as a reversal agent for neuromuscular blocks resulted in an earlier first postoperative passage of flatus compared to the use of the mixture of pyridostigmine and glycopyrrolate. Previous 2 trials on neuromuscular block reversal showed conflicting results [2,3]. In a retrospective study by Deljou et al. [2], sugammadex reversal resulted in an earlier first postoperative bowel movement in patients who underwent intraperitoneal surgery compared to reversal with neostigmine or glycopyrrolate. In contrast, a randomized controlled trial by Sen et al. [3] revealed no statistical differences in the time to first flatus or bowel movement following thyroid surgery between reversal with sugammadex and that with neostigmine or atropine.

These conflicting results may be mainly attributed to multifactorial origins of postoperative ileus. Acetylcholine allows an increase in gastrointestinal motility as the principal excitatory neurotransmitter in the gastrointestinal tract. Therefore, drug-induced cholinergic stimulation or inhibition can cause a change in gastrointestinal motility. However, because postoperative ileus is caused by complex neuro-immuno-inflammatory responses, the cholinergic pathway is one of the causative mechanisms [4]. The surgical inflammatory response and μ-opioid receptor activation are clinically more relevant pathways of postoperative ileus. Thus, reduced surgical incision or intestinal manipulation and opioid-sparing multimodal postoperative analgesia are more effective than neuromuscular reversal. In the study by An et al. [1], the magnitude of difference in the time to first flatus...
was small between the reversal with sugammadex and that with pyridostigmine or glycopyrrolate (approximately 5 h). Although it reached statistical significance, such a small difference could only have limited clinical significance.

Conflicting results among studies may also be related to the combination of different anticholinesterases (neostigmine or pyridostigmine) or anticholinergics (atropine or glycopyrrolate) and their dose regimens. Dominance of the promotility or antimotility effect on the gastrointestinal tract and its duration depends on the reversal drugs and their dose regimen. Compared to atropine, glycopyrrolate has a longer duration of action (2–4 h vs. 30–60 min). In addition, the effects of glycopyrrolate on delayed gastric emptying are greater than those of atropine [5]. Contrary to the 2 favorable studies on reversal with sugammadex [1,2], atropine was administered along with neostigmine for neuromuscular block reversal in the study by Sen et al. [3], revealing no association between the neuromuscular reversal technique and the recovery time for postoperative bowel function.

Postoperative ileus is the most common postoperative complication that delays hospital discharge, increases costs, and contributes to adverse outcomes. Various neural and chemical factors are involved in the development of postoperative ileus. In addition, considering the relatively short durations of actions of anticholinesterase and anticholinergics, the neuromuscular reversal technique may have a limited (if present) impact on the postoperative recovery of bowel function. Therefore, further studies in diverse surgical settings are required for incorporating the use of sugammadex as an element of the enhanced recovery after surgery program.

Conflicts of Interest

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

References

The following guidelines are based on recommendations from the Anesthesia Patient Safety Foundation (APSF) for working with patients who have COVID-19 [1] and the other literature [2–5], and can be modified and adapted to the circumstances of each institution or hospital. When managing patients with confirmed or suspected COVID-19 infection, it is of utmost importance to protect health care workers from infection. All medical personnel must be provided with personal protective equipment (PPE) to prevent droplet and contact infections.

Medical staff and institutions should establish procedural protocols for donning and removing PPE. Prior to patient treatment, staff must identify and review the in-hospital procedural protocols, and plan ahead for patient transfer, anesthesia work environment, and anesthesia methods.

Patient transport and operating room managing plan

- Do not allow patients to stay in the holding area. Treatment should be carried out in a pre-allocated negative pressure operating room. Warning signs for COVID-19 infection should be posted in front of the operating room to minimize staff exposure.
- Patients should not stay in the recovery room or postoperative care unit. After complete recovery in the operating room, the patient should be transferred into a negative pressure room in a ward or intensive care unit (ICU).
- Endotracheal intubation, tube exchange, and extubation are high-risk procedures that can expose healthcare workers to respiratory droplets of the virus. These procedures must be carried out in a location where negative pressure is applied such as negative pressure room, and special care should be taken.
- Depending on the clinical situation, performing an endotracheal intubation early in a negative pressure room in a ward or ICU, rather than in an operating room, should be considered.
- If it is determined that the degree of negative pressure in the environment is not sufficient, the additional application of a portable high-efficiency particulate air filter should be considered.
- A highly efficient hydrophobic filter should be placed between the endotracheal tube and the reservoir bag, to prevent atmospheric contamination by respiratory droplets during patient transfers.
Anesthesia Process

1. Preparation of manpower

- Assign the most experienced anesthesia professionals to practitioners performing endotracheal intubations. Inexperienced trainees should not perform endotracheal intubation for training purposes.
- Assign experienced assistants who can perform techniques such as cricoid pressure when performing rapid sequence induction (RSI).
- Consider allowing anesthesia teams to be replaced at least every 2 hours, to prevent fatigue.

2. Preparation before anesthesia and use of personal protective equipment

- Allow sufficient time for all staff involved to don PPE. It may take more than 5 minutes to properly wear PPE.
- Early planning and implementation of endotracheal intubation should be considered. In the event of an unexpected emergency endotracheal intubation, PPE cannot be adequately donned; therefore, early implementation should be performed when possible.
- Protective coverall/body suits, N95 masks, disposable goggles/face shields, disposable shoe covers, and disposable gloves must be worn. Use the double glove technique on both hands to reduce contact.
- A powered air-purifying respirator should be worn by healthcare workers who are involved in endotracheal intubation or extubation processes.

3. Selection of intubation technique

- Awake fiberoptic intubation should not be performed unless it is a necessary indication. Spraying local anesthetics can aerosolize the virus, and should be avoided.
- Consider using video laryngoscopes to increase the likelihood of successful endotracheal intubation.
- Consider using disposable devices for intubation.

4. Endotracheal intubation

- A high-efficiency hydrophobic filter must be applied between the face mask and the breathing circuit, or between the face mask and the reservoir bag.
- Preoxygenation for 5 minutes with 100% oxygen should be performed.
- RSI should be performed to limit procedures such as manual ventilation, which can spread aerosolized virus into the room.
- The method of RSI can be modified to suit the clinical situation. If manual ventilation is required, a small tidal volume may be considered, or a supraglottic airway may be inserted to provide ventilation instead of manual ventilation using a face mask.
- Do not use high-flow oxygen, such as high-flow nasal cannula devices, as these can aerosolize the virus.

5. Equipment management after endotracheal intubation

- All used airway equipment should be placed in double zip-locked plastic bags and removed for disposal or disinfection.
- Used laryngoscopes should be sealed in double zip-locked plastic bags as soon as the endotracheal intubation is complete, to prevent further contamination of the surroundings.
- End-tidal carbon dioxide sample lines and traps should be replaced.
- Take care to avoid contaminating various instruments in the operating room, such as stethoscopes, pens, and telephones.

6. Undressing and hand washing after endotracheal intubation

- Consider preparing additional isolation rooms as contaminated areas next to the operating room to remove and dispose of PPE in accordance with protocol. If it is difficult to obtain an additional isolation room, use the space inside or immediately outside the operating room to remove PPE according to the protocol.
- Wash your hands after removing PPE.
- Avoid body contact, including touching your hair or face, until hands are washed.

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Jong-Hwan Lee (Sungkyunkwan University School of Medicine, Seoul), WooSuk Chung (Chungnam National University College of Medicine, Daejeon), Geun Joo Choi (Chung-Ang University College of Medicine, Seoul), Jae Hee Woo (Ewha Womans University College of Medicine, Seoul), Ji Su Jang (Hallym University College of Medicine, Chuncheon), Ah-Reum Cho (Pusan National University College of Medicine, Busan).

Conflicts of Interest

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

Author Contributions

Hyun Joo Kim (Investigation; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing)
Justin Sangwook Ko (Validation; Writing – original draft; Writing – review & editing)
Tae-Yop Kim (Conceptualization; Project administration; Resources; Writing – original draft; Writing – review & editing)

ORCID

Hyun Joo Kim, https://orcid.org/0000-0003-1963-8955
Justin Sangwook Ko, https://orcid.org/0000-0003-3155-0550
Tae-Yop Kim, https://orcid.org/0000-0003-0806-8969

References

Anesthetic considerations for urologic surgeries

Chang-Hoon Koo¹, Jung-Hee Ryu¹,²

Department of Anesthesiology and Pain Medicine, ¹Seoul National University Bundang Hospital, Seongnam, ²Seoul National University College of Medicine, Seoul, Korea

Urologic surgeries are widely performed, and the cases have increased owing to the fact that the elderly population is growing. The narrow and limited surgical space is a challenge in performing most urologic surgeries. Additionally, the elderly population is exposed to the risk of perioperative complications; therefore, a comprehensive understanding and approach are required to provide optimized anesthesia during surgery. We have searched the literature on anesthesia for urologic surgeries and summarized the anesthetic considerations for urologic surgeries.

Keywords: General anesthesia; Geriatrics; Perioperative care; Postoperative complication; Spinal anesthesia; Urologic surgery.

Introduction

Most urologic surgeries are performed in a narrow and limited space with the minimally invasive technique or cystoscope, and most patients undergoing urologic surgeries are elderly individuals with other diseases. Therefore, anesthesiologists should, as well as provide adequate anesthesia, consider various factors such as age, co-morbidities, functional status, duration of surgery, predicted blood loss and surgical scope, to optimize surgical outcomes. This review aimed to provide the anesthetic considerations for various urologic surgeries.

Patients

From 1999 to 2012, in Korea, the overall incidence rates of kidney, bladder, and prostate cancer were 4.4%, 4.79%, and 7.75% [1] and generally increase with aging [2]. Owing to a growing elderly population, there has been an increase in the number of urologic surgeries, such as nephrectomy, cystectomy, and prostatectomy [3]. Surgery has been considered to be associated with higher risk of complications in elderly patients. Moreover, elderly patients tend to have comorbidities. Since these high-risk patients account for 80% of postoperative deaths [4], perioperative care, such as risk stratification, adequate intraoperative intervention, and prevention of postoperative complications, plays an important role in improving surgical outcomes, morbidity, and mortality [5].

The essential step is to identify patients who have a high risk of complications. Preoperative assessment of functional status is important because impaired physical function increases the risk of postoperative complications [6], delirium [7], and surgical site infection [8]. Patients with poor physical status should be further evaluated and pretreated to enhance functional capacity for optimized recovery [9].

Frailty reflects decreased physiologic reserve and increased vulnerability to poor health.
outcomes [10]. Several studies reported that frailty was significantly associated with postoperative mortality and morbidity in patients undergoing urologic surgery [11–13]. Therefore, preoperative frailty assessment may be useful in predicting postoperative outcomes.

Several factors associated with postoperative complications can be modified preoperatively. Smoking cessation before surgery reduces respiratory complications and promotes wound healing [14]. A smoker should be advised to stop smoking at least 4 weeks before surgery [15]. Patients scheduled for urologic surgery may have iron deficiency, with or without anemia [3]. Preoperative iron deficiency and anemia could increase the incidence of blood transfusion [3], which is reported to be associated with postoperative mortality and morbidity [16]. Therefore, treatment of iron deficiency, with or without anemia, is recommended in case of predictive blood loss > 500 ml [17]. Preoperative oral iron supplements may reduce perioperative transfusion and improve surgical outcomes.

**Nephrectomy**

Nephrectomy is a standard treatment for renal cell carcinoma (RCC). Partial or radical nephrectomy may be performed according to the tumor characteristics. The European Association of Urology guidelines recommended that patients with mass < 4 cm may undergo partial nephrectomy [18]. Since RCC commonly presents in patients aged > 70 years, most patients undergoing nephrectomy are elderly with comorbidities [19]. An evaluation of other medical conditions, such as cardiovascular, pulmonary, and cerebrovascular diseases, is required preoperatively. It could be important in estimating residual renal function because the whole or part of the kidney will be removed.

Patients are commonly placed in lateral decubitus position during nephrectomy and exposed to pressure sores, nerve damage, or venous congestion, which should be prevented with caution. For example, the eyes and ears should be protected from excessive pressure, brachial plexus injury should be prevented by applying axillary roll on the dependent side, and the neck should be placed in neutral position [20].

Since robotic surgery had been introduced into the surgical field, robot-assisted nephrectomy has gained popularity and has been increasingly performed over the decades [21]. Considerable space must be guaranteed because the robot system is heavy and bulky. The range of robot arms can be wide, so the patient’s head should be protected from unexpected collisions with the robot arms. Robot docking may disturb patient assessment and immediate management, particularly in an emergency situation. Patient movement may lead to tissue injury during robot docking [22]. Thus, sufficient neuromuscular blockade (NMB) should be considered to prevent movement or muscle contraction.

Administration of nonsteroidal anti-inflammatory drugs (NSAIDs) is commonly avoided in patients with kidney surgery due to their nephrotoxic effects. However, NSAIDs have not only postoperative analgesic effect but also opioid-sparing effect, which could decrease side effects associated with opioid use [23]. A previous study reported the favorable effects of NSAIDs in patients undergoing nephrectomy [24]. Freeland et al. [24] analyzed patients undergoing live-donor nephrectomy and found that those who received ketorolac postoperatively had less postoperative pain and shorter length of hospital stay (LOS) without reduction in renal function.

**Cystectomy**

Cystectomy is the treatment of choice for invasive bladder cancer. According to the surgical type, the whole or part of the bladder may be removed. It is a long and complicated procedure with bleeding risk. The average blood loss during cystectomy is from 0.56 to 3 L [25,26]. Therefore, blood transfusion might be considered, if necessary. However, blood transfusion was significantly associated with lower 5-year recurrence-free survival, cancer-specific survival, and overall survival in a previous study that analyzed 2,060 patients who underwent radical cystectomy [27]. Another study that included 2,934 patients who underwent radical cystectomy also revealed that perioperative blood transfusion increased morbidity and surgical site infection [28]. In contrast, Abel et al. [29] evaluated the association between the timing of blood transfusion and outcomes, and the results showed that intraoperative blood transfusion significantly increased the risk of cancer recurrence and mortality, whereas postoperative transfusion did not. In contrast to previous studies, several studies insisted the insignificant association between blood transfusion and cancer-related outcomes [30,31]. Although blood transfusion increased recurrence and mortality in the univariate analysis, this association no longer remained significant in the multivariate or adjusted analysis.

Patients with ileal conduit urinary diversion are susceptible to acid-base disorders. Hydrogen ion, chloride ion, or ammonia in the urine could be reabsorbed from the ileal conduit, which would induce hyperchloremic metabolic acidosis [32]. Van der Aa et al. [32] reported that alkalizing agents blocking chloride transport could be used to treat acid-base disorders.
Transurethral resection of bladder cancer

Transurethral resection of bladder cancer (TURB), an endoscopic procedure, is the cornerstone in the diagnosis and treatment of bladder cancer [33]. TURB is performed in a narrow and limited bladder space, and the shape, size, location, and number of tumors can be identified though the procedure. The obturator nerve running close to the lateral wall of the bladder may be stimulated during TURB, which may result in obturator nerve reflex and unpredictable movement of the ipsilateral thigh. Therefore, appropriate anesthesia should be provided for adequate surgical condition and complete resection during TURB. TURB may be performed under either general or regional anesthesia.

General anesthesia with propofol and desflurane offers more rapid induction and recovery in elderly patients undergoing brief transurethral surgery compared to spinal anesthesia [34]. NMB is needed for endotracheal intubation or supraglottic airway device. Additionally, adequate depth of NMB is required to prevent obturator nerve reflex, which causes unpredictable adductor muscle contraction. Cesur et al. [35] reviewed and analyzed 89 patients who underwent TURB from 1997 to 2007. Among them, 56 patients underwent TURB under general anesthesia and were all administered succinylcholine (depolarizing NMB agent) before resection. The authors reported that complete resection was performed in all patients. Koo et al. [36] conducted a randomized controlled trial on rocuronium (nondepolarizing NMB agent), comparing the surgical conditions and incidence of obturator nerve reflex according to the depth of NMB during TURB under general anesthesia. The authors demonstrated that deep NMB significantly increased optimal surgical condition and decreased the incidence of obturator nerve reflex compared to moderate NMB. The bladder consists of smooth muscles where NMB agents are ineffective. Therefore, it is inferred that full relaxation of surrounding muscles, including the pelvis and abdomen, could enhance surgical conditions.

Many transurethral surgeries were successfully performed under spinal anesthesia. In a previous study on patients who underwent urologic surgery, spinal anesthesia with hyperbaric bupivacaine 12 mg with 3 µg of dexmedetomidine or 30 µg of clonidine provided effective anesthetic effect with preserved hemodynamic stability [37]. Other studies showed that spinal anesthesia using levobupivacaine also offered sufficient anesthetic effect during transurethral surgery [38,39]. However, spinal anesthesia could not prevent obturator nerve reflex, and obturator nerve block (ONB) is required to prevent obturator nerve reflex. One previous study compared the incidence of obturator nerve reflex between spinal anesthesia and spinal anesthesia combined with ONB and showed that the incidence of obturator nerve reflex was lower in the patient who received spinal anesthesia combined with ONB (40% vs. 11.4%) [40].

There are various techniques for ONB, depending on the insertion point and needle direction. Fig. 1 shows the classic and inguinal approaches in ONB. Labet introduced a pubic approach, which is known as the classic approach [41]. The needle is inserted at 3 cm lateral and 3 cm inferior to the pubic tubercle and advanced to the ramus of the pubis [42]. The obturator nerve was blocked at the obturator foramen [43]. In especially obese patients or patients with blunt tubercle, it may be difficult to identify the pubic ramus, the landmark of the classic approach. The classic approach may result in injury to adjacent organs, such as the bladder, rectum, and spermatic cord [44]. The inguinal approach was first described by Choquet et al. [45] in 2005, and the needle is inserted at the midpoint of the line between the ipsilateral femoral arterial pulse and inner border of the adductor longus tendon. The obturator nerve is blocked between the adductor brevis and adductor magnus [43]. In previous studies comparing the two

Fig. 1. Comparison of the classic and inguinal approach of obturator nerve block. T: pubic tubercle, C: needle insertion point of the classic approach; I: needle insertion point of the inguinal approach.
Most prostatectomies are currently performed by robot-assisted laparoscopic radical prostatectomy (RALP), which has been widely performed to treat prostatic cancer since 1999 [51]. Other methods, such as inter-adductor approach (needle is inserted at the upper end of the adductor longus) and intravesical approach (obturator nerve is blocked through the cystoscope), have also been studied [47,48].

Transurethral resection of the prostate

Transurethral resection of the prostate (TURP) is the gold standard treatment for benign prostatic hyperplasia. Like TURB, it can be performed under either general anesthesia or spinal anesthesia. Since TURP is performed in narrow and limited spaces, irrigating fluid is used for bladder distension and sufficient surgical view. However, adverse events related to the use of irrigating fluids may occur in patients undergoing TURP [49]. Venous sinus exposure and prostatic capsule injury allow the absorption of irrigating fluid in the body. The absorbed irrigating fluid can cause acute change in the intravascular volume, electrolyte concentration, and osmolality, which leads to complications such as fluid overload, pulmonary edema, hyponatremia, and coagulopathy. Additionally, the additives of irrigating fluid, such as glycine and sorbitol, are metabolized to ammonia, which may induce tremor or seizure. This phenomenon is called TURP syndrome. The incidence rate of TURP syndrome is reported to be 1–8% [50]. TURP syndrome may cause several symptoms, including headache, anxiety, vomiting, dyspnea, arrhythmia, hypotension, confusion, seizure, and coma [51]. If any of the abovementioned symptoms occur, the anesthesiologist should suspect the development of TURP syndrome and discontinue the surgery and fluid administration. However, if patients are under general anesthesia during TURP, it is difficult to observe the symptoms of TURP syndrome. Laboratory tests may be considered to check serum sodium concentration or serum osmolality. Shin et al. [52] found that rotational thromboelastometry was useful in detecting coagulopathy caused by TURP syndrome. The treatment of TURP syndrome is supportive care, including respiratory support and anticonvulsant and adrenergic drug use. According to the severity of TURP syndrome, diuretics or hypertonic saline could be administered [51].

Prostatectomy

Since robotic surgery had been introduced to the surgical field in 1999 [53], robot-assisted laparoscopic radical prostatectomy (RALP) has been widely performed to treat prostatic cancer [54]. Most prostatectomies are currently performed by robot-assisted surgery [55]. For optimal surgical view, RALP requires 30° Trendelenburg position and high-pressure pneumoperitoneum, which moves abdominal organs to cephalad. Chest banding prevents falls. Anesthesiologists should understand the physiologic alterations caused by position, pneumoperitoneum, and chest banding. Function residual capacity and lung compliance decrease and induce ventilation-perfusion mismatch, atelectasis, and hypercapnia [56]. Several studies suggested appropriate ventilator strategies that improve oxygenation and reduce CO₂ [57]. Jo and Kwak [58] recommended pressure-controlled ventilation rather than volume-controlled ventilation to improve respiratory mechanics or oxygenation during pneumoperitoneum. Ahn et al. [59] demonstrated that the recruitment maneuver could improve intraoperative oxygenation in patients undergoing RALP. Kim et al. [60] revealed that prolonged inspiratory phase, for example, 2 : 1 and 1 : 1, could provide better oxygenation and better CO₂ elimination during pneumoperitoneum. Lee et al. [61] found that 7 cmH₂O of positive end-expiratory pressure increased oxygenation without excessive peak airway pressure. Moreover, peak airway pressure should be maintained at < 35 cmH₂O [62].

The Trendelenburg position may increase venous return and central venous pressure, which may increase cardiac output. Conversely, pneumoperitoneum may reduce cardiac output by increased systemic venous resistance. Falabella et al. [63] found slight but not significant reduction in cardiac output with the Trendelenburg position with pneumoperitoneum in patients undergoing RALP.

The Trendelenburg position could increase intracranial pressure, so a careful approach is required in patients who have a history of aneurysm or stroke. Mavrocotados et al. [64] reported that the intracranial pressure increased from 8.8 mmHg to 13.3 mmHg after a 30° head-down position. Intraocular pressure can also increase; thereby, corneal abrasion or optic neuropathy could develop [65–67]. Additionally, anesthesiologists should also consider any potential risks of the development of subcutaneous emphysema, pneumothorax, or pneumomediastinum.

During RALP, the bladder is opened to access the prostate. Since excessive urine may disturb the surgical procedure, fluid administration is restricted for optimal surgical view. Gainsburg et al. [68] insisted that < 800 ml of fluid should be administered until anastomosis of the bladder and urethra.

Nephrolithotomy and ureteroscopy

Percutaneous nephrolithotomy (PCNL) is commonly performed to treat renal stone. The indication of PCNL includes > 1.5–2 cm of renal calculi, staghorn calculi, lower pole stone, and refractory upper tract calculi [69,70]. Patients are placed in prone
position under either general or spinal anesthesia. The advantages of general anesthesia are securing airway even in prone position and minimizing pleural injury by control of tidal volume during the procedure [70]. However, there is a risk of pressure on the eyes, ears, nose, and any bony structure in the prone position. Thus, abovementioned areas should be protected throughout the surgery. In contrast to general anesthesia, spinal anesthesia may provide better analgesia and shorter recovery time [70]. The eyes, ears, and nose can be protected by the patient because they are awake during surgery. However, patients can complain of discomfort in case of prolonged surgery or insufficient anesthesia. Spinal anesthesia may aggravate unstable hemodynamics in patients with comorbidities. A recent meta-analysis revealed that the regional anesthesia group showed shorter operative time, lower postoperative pain, lesser analgesic requirements, and shorter LOS compared to the general anesthesia group [71]. However, the incidence of hypotension was significantly higher in the regional anesthesia group than that in the general anesthesia group. The stone-free and total complication rates were comparable between the two groups. The complications of PCNL include pleural injury, whose incidence rate is up to 3.1%, small bowel injury, colon injury, hepatic injury, or splenic injury [70]. Theses complications may lead to sepsis or peritonitis, unless early detection and immediate intervention are performed. During the procedure, bleeding may originate from the renal capsule or parenchyma. A potential risk for major bleeding is associated with scanty parenchyma or proximity of major vessels [69]. Srivastava et al. [72] reviewed 1854 patients undergoing PCNL and reported that 1.4% of patients underwent angioembolization due to major bleeding. Therefore, adequate hydration may be useful in maintaining stable hemodynamics.

Ureteroscopy (URS) is used to diagnose and treat problems of the urinary tract, such as ureteral stones. URS distends the renal capsule, ureter, and renal collecting system; stimulates the nociceptors; and produces pain and reflex muscle spasm. This results in flank, groin, scrotal, or labial pain. Therefore, URS should be performed under adequate anesthesia. There are several studies on URS successfully performed under local anesthesia combined with intravenous sedation [73–75]. However, several factors (short duration, small caliber, female sex, experience of the urologist, etc.) are associated with successful completion of URS [76]. General anesthesia prohibits patient movement and breathing, thereby decreasing the risk of urethral trauma. Spinal anesthesia is not preferred in patients undergoing URS because of increased induction time and delayed recovery time [76].

### Pain control and recovery

Urologic surgeries commonly produce mild to moderate pain [22]. Pain control is one of the important factors affecting the quality of recovery. There are many studies investigating various methods to alleviate pain in patients undergoing urologic surgeries [77]. In previous studies, transversus abdominis plane (TAP) block provided good analgesic effect and reduced opioid consumption in patients undergoing minimally invasive surgery [78, 79]. Local anesthetics are delivered into the layer between the internal oblique and transversus abdominis. They block sensory pathways of intercostal nerves T7–T11, subcostal nerve T12, and ilioinguinal and iliohypogastric nerves L1, which are innervated to the anterolateral abdominal wall. Baerswyl et al. [80] conducted a meta-analysis to compare the analgesic efficacy of TAP block and epidural analgesia. There was no significant difference in pain score at postoperative day 1 between the two groups, whereas the incidence rate of hypotension was significantly lower and LOS was shorter in the TAP block group compared to those in the epidural analgesia group. In another study, TAP block significantly reduced pain at postoperative day 1 and opioid consumption and shortened LOS in patients undergoing RALP [81, 82]. TAP block was also proved to decrease the first 24-h mean pain score after minimally invasive nephrectomy [79, 83–85]. Matulewicz et al. [86] reported that enhanced recovery after surgery (ERAS) protocol with TAP block improved bowel movement and decreased opioid consumption.

Since ERAS protocol had been introduced to patients undergoing colorectal surgery [87], this new approach has been applied to other types of surgeries. It is a new multimodal approach to improve preoperative status and perioperative homeostasis [88]. Patients undergoing urologic surgeries required optimized ERAS protocol because of several reasons [88]. In terms of surgical factors, urologic surgeries have longer operative time, increased risk of bleeding, and higher complication rates. Regarding patient factors, patients undergoing urologic surgeries are usually elderly with comorbidities, anemia, or malnutrition. Fig. 2 presents the ERAS protocol in patients undergoing urologic surgeries. There are still issues in reaching a consensus on the ERAS protocol in urologic surgeries, and further investigation is needed.

A urinary catheter is often placed for postoperative drainage after surgery. However, a urinary catheter usually irritates the bladder and induces patient discomfort, which is known as catheter-related bladder discomfort (CRBD) with reported incidence rate from 47% to 90% [89]. CRBD may lead to emergence agitation [90]; therefore, preventing CRBD may contribute to better quality of recovery. Several pharmacologic interventions have
operative mg parecoxib reduced the incidence and severity of CRBD postoperatively. Parecoxib, a cyclooxygenase-2 selective inhibitor, has been used to alleviate postoperative pain, and intravenous administration of 40 mg parecoxib reduced the incidence and severity of CRBD but also postoperative pain and rescue drug requirements. Nefopam, a non-opioid analgesic, inhibits reuptake of dopamine, norepinephrine, and serotonin, and 20 mg of nefopam administered before spinal anesthesia decreased the incidence and severity of CRBD [91]. Cheon et al. [92] used 40 mg of nefopam to prevent CRBD and found that intravenous nefopam could reduce not only the incidence and severity of CRBD but also postoperative pain and rescue drug requirements. Parecoxib, a cyclooxygenase-2 selective inhibitor, has been used to alleviate postoperative pain, and intravenous administration of 40 mg parecoxib reduced the incidence and severity of CRBD postoperatively [93]. Another study demonstrated that continuous infusion of dexmedetomidine reduced the incidence of CRBD [94]. Gabapentin, a structural analogue of gamma-aminobutyric acid, inhibits peripheral sensitization of afferent C-fiber, which is associated with overactive bladder, urge incontinence, and sensory urgency [95,96], and 600 mg gabapentin decreased the incidence of CRBD from 90% to 66%, while 1,200 mg gabapentin decreased the incidence from 90% to 26% [97]. Patients premedicated with glycopyrrolate also showed decreased postoperative pain, incidence, and severity of CRBD [98].

During transurethral procedures, such as TURB, TURP, or URS, intraoperative penile erection may delay the procedures and lead to complications, such as bleeding and stricture formation, although it rarely occurs (0.1–2.4%) [99]. Various strategies for intraoperative erection have been suggested. Ethyl chloride or dorsal nerve block was described as a method to reduce sensory input to the penis [100,101]. Intracavernous injection (phenylephrine, epinephrine, norepinephrine) or intravenous injection (ephedrine, dexmedetomidine, glycopyrrolate, ketamine) are described as pharmacological treatments [99]. Close hemodynamic monitoring is needed during intracavernous or intravenous injection of the drug.

**Anesthesia and cancer recurrence (general anesthesia vs. spinal anesthesia)**

Transurethral procedures can be performed under either general or spinal anesthesia, and several studies have shown that the prognosis depends on the type of anesthesia. Jang et al. [102] compared the prognosis of bladder cancer in general and spinal anesthesia in patients undergoing TURB and concluded that spinal anesthesia provided a higher 5-year survival rate than general anesthesia. Other studies also suggested that spinal anesthesia was associated with decreased recurrence rate and extended recurrence-free survival compared to general anesthesia [103,104]. These results may be because inhaled anesthetics during general anesthesia may suppress immunity, impair host defense, and proliferate malignant cells [105]. Inhaled anesthetics have been known to inhibit natural killer cell activity, monocyte phagocytosis, and tumoricidal activity [106–108], whereas they release hypoxic inducible factor-1 [105]. Hypoxic inducible factor-1 stimulates protumorigenic behavior in residual cancer cells and contributes to recurrence [105]. Another explanation of the advantage of spinal anesthesia may be attributed to the anti-metastatic effect of local anesthetics, such as lidocaine and ropivacaine, which was demonstrated in the in vitro study by Piegerle et al. [109]. However, since most transurethral procedures are relatively short, it is difficult to determine the effect of anesthesia duration on cancer recurrence and survival rate. Therefore, long-term, large-scale, and prospective investigations are needed to establish the effect of...
anesthesia on recurrence and survival rates.

Conclusion

Urologic surgeries include various spectrums of disease and elderly patients. Therefore, overall collaboration between the urologist and the anesthesiologist is required in terms of preoperative evaluation, intraoperative management, and postoperative care. An individualized, optimized approach leads to better outcomes, quality of recovery, and patient satisfaction.

Conflicts of Interest

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

Author Contributions

Chang-Hoon Koo (Conceptualization; Investigation; Methodology; Writing – original draft)
Jung-Hee Ryu (Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing)

ORCID

Chang-Hoon Koo, https://orcid.org/0000-0001-8567-5514
Jung-Hee Ryu, https://orcid.org/0000-0001-9331-5658

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Introduction

Anesthesiologists play an important role in the perioperative process by assessing the overall risk of surgery and aim to reduce the risk of complications. Perioperative hemodynamic and volume management can help to improve outcomes in perioperative patients. There has been ongoing discussion about goal-directed therapy. However, there is a consensus that fluid overload and severe fluid depletion in the perioperative period are harmful and can lead to adverse outcomes. This article provides an overview of how to evaluate the fluid responsiveness of patients, details which parameters could be used, and what limitations should be noted.

Keywords: Cardiac output monitoring; Colloids; Crystalloid solutions; Hemodynamic monitoring; Hypotension; Volume therapy.
found that there was substantial variation in the risk-adjusted mortality between European centers. These results highlight an opportunity to learn from those centers with lower risk-adjusted mortality rates to improve patient outcomes in other centers [9].

Perioperative hemodynamic and volume management are important considerations in improving outcomes in perioperative patients. There has been ongoing discussion on which fluid should be used, and at what rate it should be administered to particular patients. There is a consensus that fluid overload and severe fluid depletion in the perioperative period is harmful and leads to adverse outcomes [10]. Unfortunately, adequate management of volume therapy is challenging and requires additional testing and monitoring that is seldom used in clinical practice, even in high-risk patients [11,12].

**Physiology of volume replacement**

Adequate fluid and volume therapy during and after anesthesia is important for improving perioperative outcomes. Without a doubt, the most common intervention done by anesthesiologists is prescribing fluids. Fluids are important as normovolemia is an essential factor of hemodynamic stability and homeostasis between the intravascular fluid and extravascular space. However, the traditional concept to give fluids where hemodynamic compromise is recognized (e.g., hypotension), following the principle “in doubt give volume”, has been proven to be incorrect [13]. Notably, in abdominal surgery, the concept of “restrictive” fluid therapy that was introduced in the early 2000s was quite successful and led to better outcomes compared to the traditional liberal volume therapy [14]. In particular, complications that were associated with fluid overload like pulmonary edema, anastomotic leakage, anemia, coagulopathy, and cardiovascular compromise dramatically reduced, which led to better outcomes overall. However, in further studies, “restrictive” and “liberal” were not well defined, and what was considered restrictive in one study was deemed liberal by others [15]. In some studies, an extremely restrictive approach led to severe hemodynamic compromise with decreased perfusion, decreased oxygen delivery, and complications like acute kidney injury (AKI) [16].

Fluid overload is recognized as being harmful. Unfortunately, fluid overload is common, silent, and deadly. Bellamy [17] put together a theoretical framework based on their concept that there is a U-shape relationship between fluid therapy and outcome. Excess fluid overload and severe fluid restriction can both lead to adverse outcomes. Therefore, anesthesiologists need to find a balance and ascertain the ideal volume status for individual patients. This is termed normovolemia (Fig. 1). Two retrospective studies recently showed that fluid overload and hypovolemia are associated with unfavorable outcomes such as AKI, pulmonary complications, and even mortality [10,13]. Therefore, it is important to recognize the need for fluid in some patients and deresuscitation in others. Thus, we need to clearly define our aim when giving patients fluids. Do we want to expand the extracellular space to compensate for losses, or do we want to increase the intravascular space to improve the filling pressures and potentially cardiac output (CO)? In this review, only volume therapy, giving additional fluids to improve hemodynamic parameters, will be discussed. Fluid therapy, which is mostly used to compensate extravascular losses and regain fluid homeostasis in internal medicine patients, is beyond the scope of this article and will not be discussed.

Before giving patients additional fluid, we need to ascertain whether the issue can be solved by increasing stroke volume and cardiac output. However, usually, we do not want to increase only cardiac output. In most cases, we aim to increase oxygen delivery to the tissues. However, to achieve this, global oxygen delivery needs to first be increased. Currently, we cannot be sure that this will also lead to increased oxygen delivery to individual tissues as monitoring of the microcirculation, while possible, has not gained general acceptance in clinical practice [18]. In a review article, Monnet and Teboul [19] detailed all of the circumstances in which a volume bolus will lead to increased tissue perfusion and function. The first step is to increase the mean systemic filling pressure, which can be counteracted by capillary leakage and ven-
odilatation. The role of making artificial and natural colloids more effective so as to increase the mean systemic filling pressure has been extensively discussed. However, as yet, no conclusions have been reached. Nevertheless, colloids appear to be more able to achieve this with less fluid and a longer intravascular half-life. Therefore it is only moderately surprising that colloids, including starches, were used in 86% of the included studies in a review of fluid boluses [20]. This was done despite several studies showing that in critically ill patients, the use of colloids, and in particular starches, can result in an increased risk of renal failure and death [21–23]. However, a recent meta-analysis did not confirm these findings in surgical patients [24,25]. It is paramount that the patient is fluid responsive and that the stroke volume can be increased by additional fluid loading, given that the aim is to increase global oxygen delivery. After fluid loading, not all patients that have increases in their stroke volume and cardiac index shows better microcirculatory flow and increased oxygen consumption. Further research is needed to identify the mechanisms for uncoupling the global perfusion indices from regional indexes and identifying suitable treatment algorithms.

As optimized global perfusion is a prerequisite to optimizing microperfusion, in the following section, methods to assess the need for intravascular volume therapy to increase stroke volume will be critically discussed.

**How to assess fluid responsiveness**

The concept of determining the treatment effects of therapies is not new. If we administered vasopressors and did not measure arterial blood pressure before and after the intervention, we would be accused of malpractice. However, when we administer fluids during surgery, the verification of a positive drug effect, and the decision to give fluids is often made with little testing or indications. Almost a hundred years ago, Prof. Jarisch [26] asserted that our understanding of circulation was limited as while blood pressure is easily measured, blood flow is not. This is why blood pressure monitoring is so prevalent despite most organs requiring blood flow, not pressure. However, if we do not measure blood flow, how can we know that additional volume given to patients is actually increasing blood flow? A recent study by Cecconi et al. [27] tried to elucidate what drives the decision to give additional volume to intensive care unit (ICU) patients. In 42.7% of the patients, no testing of fluid responsiveness took place, and the decision was only based on clinical experience. In another 35.5%, the decision was based on static parameters like central venous pressure (CVP) or atrial blood pressure that we will discuss below. The second most interesting finding of this study was that despite the results of testing, about 50% in all groups (positive, negative, and uncertain) received additional fluids.

**Pressure based volume therapy – arterial blood pressure, CVP**

Generally, in recent years, a large amount of fluids has been given to patients undergoing surgery, especially when there was some sort of hemodynamic deterioration like hypotension. The idea behind this was that a “liberal” policy of fluid management in surgical patients is required. This concept is based on ideas and studies from Tom Shires, Chief of Surgery at the University of Texas Southwestern, Dallas, Texas [28]. His work led him to conclude that an extracellular fluid deficit in surgical patients and the consequent elevations of aldosterone and antidiuretic hormone is caused by extravasations of fluid from the extracellular compartment to the third space along with evaporative losses [29,30]. A strategy of aggressive fluid replacement emerged as the mainstay of perioperative care to compensate for these losses [31,32]. However, hypotension can occur quite often during surgical procedures, and in many cases, hypotension is not linked with hypovolemia. Intraoperative hypotension has been studied for many years. Therefore, it is surprising that there is still no clear definition of intraoperative hypotension. In a review by Bijker et al. [33] of 130 studies, 140 different definitions of hypotension were described. Risk factors for hypotension besides hypovolemia are increased age, a higher American Society of Anesthesiologists score, induction medication that might lead to vasodilatation, and neuro-axial anesthesia. Also, during different time frames of anesthesia, various risk factors have been published, describing post-induction hypotension, early intraoperative hypotension, and late intraoperative hypotension [34,35]. Hypovolemia is only one potential cause of hypotension. Therefore, any given arterial blood pressure cannot be used to decide whether additional fluid should be provided to a patient to increase cardiac output. Nevertheless, hypotension, in conjunction with the wider clinical picture, can help to find an indication to give fluid. In polytraumatized patients with ongoing bleeding, the first step is to give fluids. However, during procedures, it is not possible to tell when resuscitation is complete, and normovolemia is reached just by measuring the arterial blood pressure.

Another option might be to measure venous filling pressures like CVP or pulmonary artery occlusion pressure (PCWP). The measurement of filling pressures was long advocated for in many guidelines, such as the surviving sepsis campaign [36]. This guideline recommended that patients should receive additional fluids to optimize perfusion until their CVP was 8–12 or 12–15

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cmH\(_2\)O, if mechanically ventilated. Unfortunately, this has been proven to be incorrect. Filling pressures like CVP and PCWP are influenced by many other factors that are not related to the fluid status or fluid responsiveness such as cardiac compliance, intra-abdominal pressure, airway pressure and positive end-expiratory pressure (PEEP), pulmonary vascular resistance, and cardiac pathologies such as mitral/tricuspid regurgitation and congestive heart failure. Extensive research, including several meta-analyses, have been conducted on this subject and have concluded that CVP and PCWP should not be used to decide whether to give additional fluids [37,38].

Nevertheless, there is some value in measuring the CVP curve. Recent work that focused on different waves of the CVP curve found some association with preload dependence compared to no preload dependence [39,40]. However, this work must still be viewed as preliminary, particularly as no study has tested these findings with a large number of patients using a multicenter approach. Yet, the absolute number of CVP might also play an important role. Even when an absolute number of CVP does not preclude fluid-responsiveness, it can be used to assess the risk of adverse outcomes. As the CVP is the “zero-mark” of the cardiovascular system, it plays an important role in venous return and microcirculation. Therefore, severely elevated CVP values can be used as a symptom of fluid challenges, even in patients who remain fluid responsive [41]. It has been shown that CVP values over 15 mmHg are associated with increased rates of unfavorable outcomes like AKI [42].

Therefore, in these patients, CVP can be used as a marker of when to stratify increased risk versus the benefits of further fluid loading.

**Stroke volume-based volume therapy**

One easy method to test whether stroke volume can be increased through fluid loading is to give patients a defined volume bolus and measure it before and after the intervention. This concept is based on the physiological framework of Frank and Starling. Until a certain cut-off regarding the preload of the left ventricle, it can increase its stroke volume. Therefore, only patients that are below this cut-off should receive additional fluids, and this is best estimated by using the steep part of the Frank-Starling curve. Small increases in preload will lead to relatively large increases in stroke volume. Unfortunately, this cut-off varies between people and can also change during different loading conditions. This is especially troublesome as, therefore, all static parameters like filling pressures (CVP and PCWP), and volumetric measures such as global end-diastolic volume cannot provide a specific cut-off number for fluid responsiveness.

A fluid challenge is a maneuver in which a defined bolus of fluid is given within a short time frame. In most cases, this is an artificial colloid. In a recent review, it was asserted that the bolus is relatively standardized within the goal-directed hemodynamic therapy (GDT) literature, and is 250 ml [20]. In 86% of the studies, a colloid was used. It is important that the fluid bolus is given relatively rapidly so that it can stretch the right ventricle to detect an increase in stroke volume in responders. Therefore, most authors apply the bolus within 5–10 minutes or less. If the bolus is too small or given too slowly so that an acute increase of the right ventricular end-diastolic volume is not reached, there is a risk of a false negative test. Most authors recommend measuring stroke volume before and after the fluid challenge. An increase in stroke volume of at least 10–15% is considered a positive response [43]. Theoretically, any device that can measure stroke volume could be used. However, most studies use uncalibrated pulse wave analysis technology.

A fluid challenge is included in many algorithms used to optimize hemodynamics, also called hemodynamic GDT [44]. One of the simplest algorithms is to measure stroke volume, give a fluid challenge, and repeat this until the stroke volume no longer increases by more than 10%. These simple algorithms are easy to follow with high implementation rates. However, if the trigger is hypotension, repeated negative fluid challenges, especially in the ICU, can lead to a substantial positive fluid balance. An unsuccessful fluid challenge does not significantly increase stroke volume and, therefore, might decrease oxygen delivery due to inherent hemodilution if blood is not used for the fluid challenge.

**Volume therapy based on dynamic parameters**

Another way to optimize the fluid status of patients is by using dynamic parameters like stroke volume variation (SVV), pulse pressure variation (PPV), or pleth variability index (PVI). The dynamic preload parameters, SVV and PPV, are based on changes in the arterial pressure waveform due to changes in stroke volume in relation to positive pressure ventilation. The PVI is an algorithm that allows for the continuous and automatic estimation of respiratory variations in the pulse oximeter waveform amplitude to assess fluid responsiveness. To use these parameters for GDT, it is mandatory to continuously measure the blood pressure or the pulse oximeter waveform amplitude. Today there are a variety of technologies available that can measure this invasively and non-invasively. Various studies have shown that SVV and PPV are better predictors of fluid responsiveness than the static parameters CVP, PCWP, and mean arterial pressure (MAP). SVV (area under
the curve [AUC] 0.84) and PPV (AUC 0.94) are good predictors of fluid responsiveness with clinically acceptable levels of sensitivity (0.82 and 0.89) and specificity (0.86 and 0.88) [45]. The cut-off for SVV has been published to be between 10% and 12% [46]. Benes et al. [47] investigated the hemodynamic goal-directed protocol based on SVV in high-risk surgery patients undergoing an elective abdominal operation. The results showed that the GDT-group had better intraoperative hemodynamic stability, a decrease in serum lactate at the end of the surgery, and a lower incidence of postoperative organ complications in comparison with the control group.

Scheeren et al. [48] investigated a combination of SVV and stroke volume optimization in 64 high-risk surgery patients, which were divided into two groups. The primary outcome measure was the number of postoperative complications. The authors could show that an SVV and stroke volume optimization protocol is feasible and can decrease postoperative wound infections. The number of patients with at least one complication (46% vs. 62%) and the number of postoperative complications per patient tended to be lower in the study group.

Other studies investigated PPV as a goal for GDT. The best cut-off value for predicting fluid responsiveness has been published to be between 10% and 15% [49]. Salzwedel and colleagues [50] performed a multi-center study in 160 patients undergoing major abdominal surgery and showed that hemodynamic GDT using PPV, cardiac index trending, and MAP led to a significant decrease in postoperative complications.

Even though the dynamic parameters are better predictors of fluid responsiveness, they have some significant limitations. First, the patient needs to be mechanically ventilated without spontaneous breathing. The published cutoffs in fluid responsiveness for SVV and PVV were validated in patients with a tidal volume > 8 ml/kg. So, if the patient is ventilated with a lower tidal volume, the patient may be false negative for volume responsiveness. Another limitation is that it can display a slow heart rate/respiratory ratio. In patients with extreme bradycardia or high respiratory rate (e.g., high-frequency ventilation), the results may be falsely negative for predicting fluid responsiveness. Another special situation is patients undergoing open-chest procedures. In such situations, the PPV (AUC 0.55) and SVV (AUC 0.49) show a low predictive power and should also be used with caution because the results may be falsely negative [51]. In spontaneous breathing patients and patients with arrhythmia, dynamic parameters cannot be used as ventricular filling depends on the variation of diastolic filling in severe arrhythmia, and there is no controlled stimulus in spontaneous breathing patients.

Volume therapy based on physiologic testing

Passive leg raising (PLR)

Widely known for treating acute circulatory failure, passive leg raising (PLR) has gained increasing interest in the perioperative prediction of fluid responsiveness. PLR is a safe method for reversible and rapid autotransfusion of approximately 300 ml of blood without the need for further fluid bolus [52,53]. Since the accuracy of PLR is not dependent on a sinus rhythm or high tidal volume, ventilation can also be applied when dynamic preload parameters are not viable. On the other hand, surgical procedures which are not compatible with the movement of legs or the Trendelenburg position (e.g., neurosurgery, orthopedic surgery of the lower limbs) represent relative contraindications for PLR.

Even though most studies investigating PLR derive from critically ill patients, the predictive value can also be assumed for perioperative patients. A meta-analysis that summarized 23 studies investigating the diagnostic accuracy of PLR (measured with flow-based hemodynamic monitoring tools) showed that the pooled sensitivity of PLR was 86% (95% CI: 79%–92%), while its specificity was 92% (95% CI: 88%–96%). This shows its high diagnostic performance in predicting fluid responsiveness [54]. A second systematic review of 991 patients was able to confirm these findings but emphasized the need to measure CO as a target parameter in order to achieve reliable results [55]. It must be highlighted that PLR can be used to decide whether fluid therapy is needed or not. However, even though its practical implementation appears to be simple, some pitfalls have to be thoroughly considered to increase its predictive accuracy. Monnet and Teboul [53] summarized these as; The measurement starts from the semi-recumbent and not from a supine position and should target CO or its indices as opposed to blood pressure. CO can be assessed with different devices (e.g., echocardiography, pulse contour analysis), but it is of high importance that the measurements can detect rapid changes (< 1 min). Furthermore, the procedure does not end by the patient’s reposition but with a postinterventional observation period until the hemodynamic situation has been normalized. The depth of anesthesia should be appropriate to avoid sympathetic activation, and adrenergic stimulation blurring the effect of PLR. If these factors are taken into consideration, PLR can be considered a powerful diagnostic tool for predicting perioperative fluid responsiveness and is recommended by several international guidelines [56–58].

End-expiratory occlusion test (EEOT)

A decade ago, Monnet et al. [59] introduced EEOT. The underlying principle of EEOT is based on the influence of deep inspira-

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tion on cardiac preload. By carrying out a short (15–30 seconds) end-expiratory occlusion in mechanically ventilated patients, CO is impaired while the atrial filling is simultaneously facilitated, leading to an increase of ventricular stroke volume. To receive a reliable prediction of fluid responsiveness, continuous CO measurement is necessary during EEOT [60]. Furthermore, an EEOT-induced change of 5% of CO is generally accepted as proof of fluid responsiveness [60]. Pulse contour analysis superiorly performs to echocardiography in terms of the precise detection of CO changes during EEOT [61]. However, other devices such as echocardiography, non-invasive CO measurements, and Doppler-based methods are feasible but need more confirmative studies [20, 62, 63].

EEOT imitates a fluid challenge without the need for fluid application. In contrast to the PLR test, the patient does not need to be moved, making it an attractive solution for surgery. Its predictive value was confirmed in several studies for patients ventilated with tidal volumes ≥ 8 ml/kg. However, its accuracy in patients ventilated with smaller tidal volumes is still being debated [20, 59, 60, 64–66]. Most studies investigating EEOT under low-tidal volume ventilation derive from an intensive care setting and cannot be directly transmitted to surgery [65, 67]. Only one study involving neurosurgical patients directly compared the effects of low- to regular-tidal volume ventilation on the accuracy of EEOT, and showed a very low predictive value of EEOT under low-tidal volume ventilation (AUC of the change of cardiac index 0.53 [95% CI: 0.35–0.71]) [68]. Guinot et al. [66] published the only study showing a low predictive value of EEOT for fluid responsiveness under sufficient tidal volumes (of 8.2 ml/kg) in a heterogeneous study of surgical patients. The reason for these findings remains unclear, but differences between the perioperative and intensive care ventilation strategies might be a factor. However, it has been shown that the level of PEEP does not affect the reliability of EEOT [69].

**Novel physiological tests for predicting fluid responsiveness**

End-tidal carbon dioxide concentration (PET\textsubscript{CO}\textsubscript{2}) is a surrogate for CO and is well-known for detecting successful cardiopulmonary resuscitation. It has been shown that PET\textsubscript{CO}\textsubscript{2} directly correlates to CO and can sufficiently predict fluid responsiveness when combined with PLR testing [70, 71]. Tusman et al. [72] introduced a further method based on volumetric CO\textsubscript{2} measurements by quantifying the amount of exhaled CO\textsubscript{2} instead of the concentration. To detect a lack of intravascular fluids, the patient’s fluid responsiveness was provoked with an elevation of PEEP from 5 to 10 cmH\textsubscript{2}O for one minute. During this, patients were monitored with volumetric capnography and pulse contour analysis. Afterward, patients received 500 ml of crystalloids, and the measurements were repeated. A decrease of exhaled CO\textsubscript{2} volume during the PEEP challenge was predictive of fluid responsiveness. Furthermore, a ROC-analysis revealed a high predictive performance that was superior to the change of end-tidal CO\textsubscript{2} concentration and PPV. Even though this method is only available in ventilated patients, it offers a non-invasive and accurate approach for predicting fluid responsiveness that is worthy of further validation [72, 73].

In 2005, the respiratory systolic variation test (RSVT) was introduced for predicting fluid responsiveness in surgical patients [74]. The RSVT is performed through the application of three consecutive inspiratory breaths with increasing peak inspiratory pressures (of 10, 20, and 30 cmH\textsubscript{2}O) and the simultaneous detection of the three lowest systolic arterial pressures. Next, this blood pressure is correlated to the peak pressure of the inspiratory breath, resulting in an RSVT slope. The slope corresponds to the Frank-Starling curve-enhancing a physiologic comprehension of the fluid challenge and is comparable to PPV and SVV in predicting fluid responsiveness [74, 75].

**Deresuscitation strategies using monitoring of volume status**

Originally, the term deresuscitation was used to describe a strategy that aimed to treat fluid overload following the resuscitation and stabilization of critically ill patients. Fluid therapy is used to restore the intravascular volume homeostasis to achieve sufficient tissue oxygenation and can be characterized by the Resuscitation, Optimization, Stabilization, and Evacuation (ROSE) concept [76, 77]. First, patients must be resuscitated from circulatory shock (resuscitation). To avoid adverse outcomes associated with fluid overload, fluid responsiveness should be guided by validated tests such as PLR and EEOT (optimization and stabilization). After stabilization of the patient’s hemodynamic status, de-escalation should be considered early and monitored with tests for fluid responsiveness (evacuation) [76]. The goal of the evacuation, deresuscitation phase, is to restore the patient’s physiologic homeostatic intravascular balance and to eliminate superfluous fluids. In the intensive care setting, this can be performed with restrictive volume therapy, diuretics, and/or renal replacement therapy. It has been shown that a negative fluid balance over three days predicts an improved ICU survival rate [76–78]. However, two questions arise: First, what is the best approach to guide deresuscitation, and second, should we consider deresuscitation strategies in the perioperative setting?

To treat fluid overload, it first has to be accurately diagnosed. Assuming that fluid non-responders reflect patients with balanced or overloaded fluid status, a possible approach could be to identify...
them using fluid responsiveness tests. Since these patients do not benefit from a volume challenge, it can be assumed that CO does not decrease through fluid removal. Besides, fluid removal can be performed until the fluid responsive tests return positive results. In addition to PLR and EEOT, dynamic preload parameters, body weight quantification, bioimpedance measurements, and respiratory variations of the diameter of the inferior cava vein have been evaluated as treatment goals for deresuscitation [73, 76, 79–83]. To reduce adverse outcomes after acute lung injury, Cordemans et al. [84] used intra-abdominal pressure and the extravascular lung water index to guide the treatment protocol. This consisted of high PEEP levels, small volume resuscitation with albumin, and fluid removal (PLA - treatment, [PEEP, albumin, and Lasix*]). However, the role of albumin in critically ill patients has to be further investigated because two prospective studies failed to show a beneficial effect of albumin therapy [85, 86]. While the Furosemide and Albumin for Diuresis of Edema study failed to proof feasibility [86], the Albumin Italian Outcome Sepsis study showed no improvement in the 90-day survival rate after targeting an albumin plasma level ≥ 30 g/L over 28 days after septic shock [85].

Since the phases of ROSE do not generally apply to surgical patients, it cannot be directly adopted in the perioperative setting. However, it is well-known that perioperative fluid overload is associated with adverse outcomes and should be avoided [87–89]. Hence, smart perioperative volume therapy should prevent fluid overload and the need for perioperative deresuscitation. Over the last decade, several GDT protocols have been introduced and evaluated. A recent meta-analysis summarized 95 randomized-controlled trials and was able to show a GDT-induced reduction in mortality, morbidity, and length of hospital stay [90]. Contrastingly, the Optimisation of Cardiovascular Management to Improve Surgical Outcome (OPTIMISE) study was not able to prove the benefits of GDT [88]. The OPTIMISE study protocol aimed to maximize CO by optimizing it individually with fluids until no increase of stroke volume was detectable with further support from doxepamine. Since no reduction of mortality or morbidity was detected, it can be questioned if a maximized CO target is reasonable. Additionally, it is unclear as to whether patients should receive fluids until their preload capacity is completely exploited [73, 91]. Hence, modern GDT protocols do not aim for a maximized CO but rather utilize personalized hemodynamic GDT management with multiple parameters for assessing blood flow and fluid responsiveness [91]. Even though the beneficial effects of personalized GDT are indisputable, only a small degree of patients receive this hemodynamic management. This highlights the need for its greater implementation in daily anesthetic routines [12].

Fluid overload is a common issue following the stabilization of critically ill patients. Deresuscitation strategies using tests for fluid responsiveness as well as hyperoncotic infusion combined with diuretics, and renal replacement therapy, might help to remove the extra fluids and increase survival. However, further high-quality studies are required to confirm these findings. Furthermore, the role of deresuscitation must be discussed in terms of intensifying actions for preventing perioperative fluid overload. To achieve this, personalized hemodynamic treatment goals combined with GDT protocols appear to be an effective approach.

**Conclusions**

Adverse outcomes after surgery are still common, with surgery considered one of the leading causes of death. Many prospective and retrospective studies have shown that volume management and fluid overload can have detrimental effects on postoperative outcomes. Therefore, strategies that help to prevent fluid overload and assess the individual need for volume during and after surgery should be implemented to increase patient safety. In many patients, no monitoring of volume therapy is performed, or inadequate statistical parameters are used, such as arterial blood pressure, venous filling pressures, or volumetric parameters that cannot assess fluid responsiveness. As a gold standard to assess whether patients can benefit from an increase of stroke volume and, therefore, potentially by an increase in oxygen delivery, dynamic testing should be performed. This can be done using dynamic parameters like SVV or PPV or by forced manipulation of the preload, e.g., by a volume challenge, PLR, or another physiological testing method.

In combination with a goal-directed hemodynamic monitoring protocol and the application of vasopressors and inotrope medication, a reduction of mortality by 58 was observed in a recent meta-analysis [90]. Whether goal-directed volume therapy can reduce perioperative mortality still needs to be demonstrated in larger multicenter studies. Whether the concept of using suitable parameters for goal-directed deresuscitation reduces complication rates, and mortality in the perioperative setting still awaits confirmation by larger trials. Nevertheless, this concept appears to be promising.

**Conflicts of Interest**

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

**Author Contributions**

Michael Sander (Conceptualization; Supervision; Visualization;
Writing – original draft; Writing – review & editing
Emmanuel Schneck (Conceptualization; Visualization; Writing – original draft; Writing – review & editing)
Marit Habicher (Conceptualization; Visualization; Writing – original draft; Writing – review & editing)

ORCID
Michael Sander: https://orcid.org/0000-0003-1677-3609
Emmanuel Schneck: https://orcid.org/0000-0003-0565-1550
Marit Habicher: https://orcid.org/0000-0001-8964-3819

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Tips for troublesome sample-size calculation

Junyong In¹, Hyun Kang², Jong Hae Kim³, Tae Kyun Kim⁴, Eun Jin Ahn⁵, Dong Kyu Lee⁶, Sangseok Lee⁷, Jae Hong Park⁸

Department of Anesthesiology and Pain Medicine, ¹Dongguk University Ilsan Hospital, Goyang, ²Chung-Ang University College of Medicine, Seoul, ³Daegu Catholic University School of Medicine, Daegu, ⁴Yangsan Hospital, Pusan National University School of Medicine, Busan, ⁵Inje University Seoul Paik Hospital, Inje University College of Medicine, ⁶Guro Hospital, Korea University School of Medicine, ⁷Sanggye Paik Hospital, Inje University College of Medicine, Seoul, ⁸Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

Properly set sample size is one of the important factors for scientific and persuasive research. The sample size that can guarantee both clinically significant differences and adequate power in the phenomena of interest to the investigator, without causing excessive financial or medical considerations, will always be the object of concern.

In this paper, we reviewed the essential factors for sample size calculation. We described the primary endpoints that are the main concern of the study and the basis for calculating sample size, the statistics used to analyze the primary endpoints, type I error and power, the effect size and the rationale. It also included a method of calculating the adjusted sample size considering the dropout rate inevitably occurring during the research. Finally, examples regarding sample size calculation that are appropriately and incorrectly described in the published papers are presented with explanations.

Keywords: Biostatistics; Effect size; Independent t-test; Power; P value; Sample size.

Introduction

A well-established sample size is very important for presenting, analyzing, and drawing conclusions. However, determining the sample size is one of the challenges in research design [1]. If the calculated sample size is inadequate or not described properly, it is difficult to avoid a negative review and the findings of the study would not be accepted. In this paper, along with some explanation to help understand sample size, several examples of incorrectly described and well-described cases of sample size calculation are presented. The subjects of this study were randomized controlled studies published in the Korean Journal of Anesthesiology (KJA) 2018–2019 and Anesthesia and Pain Medicine (APM) 2019. All explanations were described for the t-test to distinguish the difference between the means of the continuous variables in two independent groups, based on two-tailed test, significance level of 0.05, and power of 80%. For a detailed explanation, refer to the papers by Kim and Park [1], Kwak and Kim [2], and Kim [3].

The following factors are needed to calculate the sample size of a randomized controlled study.
Effect size, significance level, and power

The effect size or treatment effect is the difference between groups that investigators try to observe. It is the minimal difference determined to be meaningful. However, the size and unit of the effect size vary depending on the observation variable. For example, a study comparing the hypertensive effects of two antihypertensive drugs could set the effect size to be an average difference of 20 mmHg. As another example, if you compare the heights of men between two regions, the effect size could be set to an average difference of 5 cm. Standardization is necessary to use these various effect sizes (treatment effects) in calculating sample size [4–6].

One of the typical standardized effect size is Cohen’s d, which divides the difference in mean by the pooled standard deviation (Equation 1) [4–6]. Through standardization, the sample size can be calculated regardless of the nature of the observed variables. In the hypertensive drug study described above, the standardized effect size can be obtained by dividing the mean difference of 20 mmHg by the standard deviation of blood pressure. Also, in the study of male height by region, the standardized effect size is calculated by dividing the average difference of 5 cm by the standard deviation of the height.

\[
Cohen's\ d = \frac{mean\ difference}{pooled\ standard\ deviation}\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ (Equation\ 1)
\]

The second important factor is the significance level. When comparing the two groups, it is well known that analysis by random sampling is often performed because full surveys are frequently impossible. Even though there is no difference between the two groups, Type I error can be found due to the limitation of the analysis by sampling, rejecting the null hypothesis of “no difference.” For statistical analysis, it is necessary to set the probability to allow Type I error, which is called a significance level (α). In clinical studies, the significance level is usually 5% [4,7]. In the statistical analysis, if the P value is lower than the significance level, the zero hypothesis of “no difference” is rejected and the alternative hypothesis, “there is difference” is adopted. Power is important here. Power is the probability that the alternative hypothesis is true in the statistical analysis when the alternative hypothesis is really true. If the power is set low, it means that the alternative hypothesis is less likely to be true even if the alternative hypothesis is adopted, so it is difficult to trust the result that the alternative hypothesis is true. This is because the Type I error may have occurred. In order to avoid this risk, power should also be adequate. Clinical studies usually specify power at 90% or 80% [7].

Finally, what happens if we adopt a larger sample size than is calculated by specifying a typical effect size, significance level, and power? Or what if we recruit more subjects during the study than the sample size established in the study design? Under the same conditions3, as the sample size increases, the power increases as well as the probability of statistical significance. This is because increasing the sample size reduces the standard error (Equation 2).

\[
Standard\ error = \frac{s}{\sqrt{n}} \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ (Equation\ 2)
\]

For this reason, the researcher may be tempted to include an unnecessarily large number of subjects at the design stage, or to add subjects if significant results have not been obtained despite the recruitment of the proposed number of subjects. However, a breach of the study design initially established causes a number of biases and lowers confidence in the results of the study. To avoid this risk, the journal requires the approval number of the Institutional Review Board (also known as an independent ethics committee, ethical review board, or research ethics board) and the registration number given on the official website5.

To illustrate the importance of a carefully determined sample size, let’s take an extreme example. Compared to the existing surgery method (500,000 won, control), the new surgery method (5 million won, experimental group) is expensive, but hypothesized to significantly shorten the hospital stay. The study recruited 10,000 participants each to the control and experimental groups. The average length of hospital stay, which was 7 days, was shortened by 10 minutes in the experimental group and was statistically significant. Although a 10-minute reduction in length of stay is statistically significant, it may not be clinically meaningful. Rather, if the sample size was only determined to get a significant statistical result, it will be difficult to avoid accusations of incurring unnecessary physical and economic losses to patients in the study. In addition, waste of research resources such as research expenses and input of research personnel cannot be ignored. Therefore, the sample size should be carefully determined from the design stage, taking into account not only statistical significance but also cost-effectiveness, ethical concerns regarding the patient, and...

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1) For the sake of understanding, the text is based on the comparison of the mean of continuous quantitative variables between two independent groups. Nevertheless, it is necessary to select an appropriate formula to calculate the effect size according to various observations, statistical methods and the number of groups.

2) Although the alternative hypothesis is true, there are also errors that reject the alternative hypothesis, which is called a Type II error.

3) In the same study, the same effect size and significance level are maintained.

4) Relevant clause of this journal in the RESEARCH AND PUBLICATION ETHICS section is as follows: “4. Registration of the clinical trial research - Any research that deals with clinical trial should be registered with the primary national clinical trial registration site such as Korea Clinical Research Information Service (cris.nih.go.kr/) or other sites accredited by WHO or International Committee of Medical Journal Editor such as ClinicalTrials.gov (clinicaltrials.gov);”
clinical significance.

Dropout rate

Participants are dropped from studies for a variety of reasons. Therefore, an adjusted sample size with a dropout rate is required to better understand the characteristics of each study and to ensure power even after some subjects drop out [4]. A common error in the dropout rate calculation is that the additional recruits are simply calculated by multiplying the sample size by the dropout rate (Equation 3). When the adjusted sample size including the dropout rate is multiplied by the dropout rate, the sample size we want to obtain should be arrived at (Equation 4).

\[
\text{Miscalculated adjusted sample size} = \text{calculated sample size} \times (1 + \text{dropout rate}) \quad \text{(Equation 3)}
\]

\[
\text{Adjusted sample size} = \frac{\text{calculated sample size}}{1 - \text{dropout rate}} \quad \text{(Equation 4)}
\]

For example, suppose we need 500 subjects for the targeted power and expect a 10% dropout rate during the study. It is a miscalculation to determine that 550 are needed participants by simply adding 50, which is 10% of 500. As there should be 500 remaining individuals after 10% dropout,

Initial recruitment \times (1 – 0.1) = 500

(1 – 0.1) to the right-hand side,

Initial recruitment = \frac{500}{(1 – 0.1)} = 555.56

Rounding up 555.56 would result in 556 subjects.

Status of sample size description in published papers

In the KJA from vol. 71, no. 1, 2018 to vol. 72, no. 5, 2019. 31 randomized controlled clinical studies were included. APM included 13 of the papers published in vol. 14, no. 1 to 3 in 2019. A total of 44 papers were divided and reviewed by members of the Statistical Round in KJA. Afterwards, the plenary session finally decided whether the reviews were appropriate\(^5\). The following items were examined to confirm the calculation and description of the sample size:

- Is the primary endpoint clearly defined?
- Are the primary endpoint and the statistics used to calculate the sample size consistent with each other?
- Is the rationale or reference of the effect size adequately described?
- What level of significance and power is selected?
- Is the dropout rate appropriate, and is the final sample size properly calculated?
- Is the entire calculation process appropriate and without error?

In looking for the primary endpoint, the statistics applied to it were also reviewed. Table 1 shows the types of statistics used in 44 papers. The table shows different frequencies between the statistics used in the primary endpoint and those used in the sample size calculation. The t-statistic was used more than the F-statistic in the calculation of sample size compared to the analysis of primary outcome. This is probably because the t-statistic between any two groups was obtained without using the F-statistic in order to avoid complex calculations in comparative studies for three or more groups. In addition, in the sample size calculation, there was one case where the technique is not clear but is estimated to use z-statistics, and there were two cases classified as "Others" because it was impossible to figure out the statistics used.

In most cases, the primary outcome was suggested, but in some papers it was difficult to determine it because multiple outcome variables were listed without explicit description. In such cases, the variable used to calculate the sample size was determined as the primary outcome. Even if non-parametric statistical methods were applied because the primary outcome data did not satisfy the normality assumptions, they were classified as parametric (e.g., t-test for Mann-Whitney). Even if several variables are analyzed in the study, the calculation of the sample size should be done on the primary outcome.

Table 2 summarizes the effect size description. Table 2-A shows the basis for determining the effect size. Table 2-B shows whether the statistics of the effect size needed to calculate the sample size are presented properly. For example, in an experimental-control study comparing mean between two groups, the mean of each

| Statistics Used to Evaluate Primary Outcomes and Calculate Sample Size in the Collected Studies |
|-----------------------------------------------|--------------------|--------------------|
| For primary endpoint | For sample size calculation |
| t statistic | 23 (52.2) | 25 (56.8) |
| F statistic | 8 (18.1) | 5 (11.4) |
| Chi statistic | 13 (29.5) | 11 (25.0) |
| z statistic | 0 (0) | 1 (2.3) |
| Others | 0 (0) | 2 (4.5) |
| Total | 44 (100.0) | 44 (100.0) |

Values are presented as absolute number of articles (%).

\(^5\)With this procedure, kappa is not presented even if multiple members review the papers.
group (or the difference between the mean of the two groups), the standard deviation, or the incidence of events in each group should be described. If only some of these values are described and it is not possible to determine whether the sample size calculation is appropriate, they are classified as incomplete. Eight cases had no mention of the effect size (Table 2-A), and 11 cases did not describe the actual value, even though the effect size was mentioned. Thirteen cases were unable to calculate the sample size because they were not detailed enough.

Except for a case of missing description, 0.05 was chosen as the significance level (Table 3). The majority of the studies (77%) had 80% for power, but few (18%) had 90%. In one case, 99% power was chosen. As described above, power increases as the sample size increases at the same significance level. This is hard to see in clinical studies. It is possible that an overly large sample size was set in the study design or additional individuals were recruited during the study to obtain significant results.

Fig. 1 summarizes the dropout rates presented in the papers, ranging from 5–20%. Eighteen of the 44 cases were appropriate and the sample size calculation process was clearly described. Miscellaneous errors included the cases where the primary end-point is unclear, there is no value of dropout rate even though it is described to be reflected in the calculation process, there is no data of the primary endpoint regarding sample size calculation, or there are calculation errors other than the dropout rate.

Finally, it was checked whether all of the steps mentioned above were executed properly to yield the correct sample size. Of the 44 cases, 9 had all the techniques and calculations properly carried out. There were 15 cases where it was impossible to determine whether the calculation was adequate due to insufficient records, and 20 cases where all parts were recorded but the calculation was incorrect.

Inappropriate and appropriate examples of sample size calculations

In this section, excerpts of sample size calculations from published papers are presented, giving examples that are inappropriately described and examples that are appropriately described. Some of the contents are modified for better understanding.

1. Undefined primary outcome

The above two sentences describe the primary outcome in each study design.

In the first study, the pain described by the Numeral Rating Scale at 6 hours after surgery as the primary outcome is not clear. There is no specific description such as postoperative pain or sore throat after tracheal tube extubation. In addition, the baseline time point for the 6-hour passage is not clear.

The second study was designed to detect 50% differences in group anal analgesia. However, the criteria for a 50% reduction are not described—whether the dose of analgesic is decreased or the frequency of administration is reduced—and again, the base-

<p>| Table 2. Sources of the Effect Size and Relevance of Description |</p>
<table>
<thead>
<tr>
<th>No. (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Source of the effect size</td>
</tr>
<tr>
<td>Reference</td>
</tr>
<tr>
<td>Pilot study</td>
</tr>
<tr>
<td>No description</td>
</tr>
<tr>
<td>B. Relevance of description</td>
</tr>
<tr>
<td>All values are described completely</td>
</tr>
<tr>
<td>Absence of values in spite of mentioning the source of effect size</td>
</tr>
<tr>
<td>Cases in which sample size cannot be calculated because only partial values are presented</td>
</tr>
</tbody>
</table>

Values are presented as absolute number of articles (%).

<p>| Table 3. Summary of Significance Level and Power Applied in the Literatures |</p>
<table>
<thead>
<tr>
<th>No. (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significance level</td>
</tr>
<tr>
<td>0.05</td>
</tr>
<tr>
<td>not applicable</td>
</tr>
<tr>
<td>Power (%)</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>99</td>
</tr>
<tr>
<td>not applicable</td>
</tr>
</tbody>
</table>

Values are presented as absolute number of articles (%).
line for 6 hours is not clear.

2. Missing standard deviation

To detect a difference in mean time to first bowel movement of 24 hours, a sample size of 28 in each group was calculated, with power of 80% and 5% level of significance (two-tailed). Based on a report, the reduction in mean time was 15.1 hours.

To determine the effect size, the difference between the means of the two groups and the standard deviation of each group are needed. In this case, it was not possible to confirm whether the described sample size was calculated because the standard deviation was not presented (Equation 5).

\[
 n_1 = n_2 = \left( \frac{z_{\alpha/2} + z_{\beta}}{s^2} \right) \frac{2}{d^2} = \left( \frac{1.96 + 0.84}{15.1^2} \right) \quad \text{(Equation 5)}
\]

3. Missing mean difference and standard deviation

Based on a previous study, a sample size for two groups was 40 patients to demonstrate 40% mean difference with 80% power and 5% level of significance. To allow for study error and attrition, 60 patients were included in this study.

In this case, the mean difference and the group standard deviation are not described in the text. It is not possible to calculate the sample size only by the ratio of the differences between the groups (Equation 6).

\[
 n_1 = n_2 = \left( \frac{z_{\alpha/2} + z_{\beta}}{s^2} \right) \frac{2}{d^2} = \left( \frac{1.96 + 0.84}{0.4^2} \right) \quad \text{(Equation 6)}
\]

Although the cited reference includes the value, it is difficult for the reader to determine which value, so the value used should be described in detail.

4. Missing specific values in comparison of incidence rates

Assuming that drug A would reduce the incidence of nausea by 50%, we would need 30 patients in each group (80% power, 5% level of significance).

Only 50% reduction is described without baseline incidence of control group. If the incidence of the control group is 50%, the incidence of the treatment group is reduced by 50% to 25%, and 74 participants are required. If the incidence of the control group is 40%, the incidence of the treatment group is reduced by 50% to 20%, and 105 individuals are required (Equation 7, 8). Inferring in 30 patients would result in a 77% incidence of controls (Equation 9), but no source for 77% was given in the text.

\[
 n_1 = n_2 = \left( \frac{1.96 + 0.84}{0.25^2} \right) \quad \approx \quad \text{74} \\
 n_1 = n_2 = \left( \frac{1.96 + 0.84}{0.2^2} \right) \quad \approx \quad \text{105} \\
 n_1 = n_2 = \left( \frac{1.96 + 0.84}{0.385^2} \right) \quad \approx \quad \text{30} \\
\]

(Equation 7, 8, 9)
5. Calculation error

Based on a previous study, the incidence of pain in the control group was assumed to be 70%; we considered a 40% reduction in pain to be clinically significant. The minimum sample size for each group was 29 patients assuming 5% significance level and 90% power using the two-tailed Z test for proportions.

First, the subject of the 40% reduction is not clear. If there is a 40% reduction in the incidence of the 70% of the control group (0.7 × 0.4 = 0.28), the incidence of the treatment group is 42% (0.7 – 0.28 = 0.42). Substituting this incidence, the sample size is 61 instead of 29 (Equation 10). Alternatively, if 40% means the difference between the incidence of 70% of the control group and 30% of the incidence of the treatment group, 28 are calculated (Equation 11).

\[
\begin{align*}
  n_1 &= n_2 = \frac{(1.96 + 1.28)^2 \times (0.7(1 - 0.7) + 0.42(1 - 0.42))}{0.28^2} \approx 61 \\
  n_1 &= n_2 = \frac{(1.96 + 1.28)^2 \times (0.7(1 - 0.7) + 0.3(1 - 0.3))}{0.4^2} \approx 28
\end{align*}
\]

(Equation 10) (Equation 11)

Even when all the values necessary for calculation are described, there can be errors in calculation. Therefore, in order to secure the reliability of the results, a careful examination of the calculation process is required.

6. Dropout rate

The sample size of 39 patients in each group was calculated with 90% power and 5% significance level. The final sample size consisted of 43 patients to allow for a 10% dropout rate.

Forty-three participants were presented, adding 10% to 39. However, the sample size remaining after dropout rate should be 39.

\[
\text{Adjusted sample size} = \frac{\text{Calculated sample size}}{1 - \text{dropout rate}} = \frac{39}{1 - 0.9} = 43.33
\]

(Equation 12)

The result is 43.33, but the value after the decimal point should be rounded up to one person (Equation 12).

That is, 44 subjects, not 43, should be recruited.

https://doi.org/10.4097/kja.19497

7. Proper description

“The primary outcome of this study was the time required to inset the device successfully on the first attempt, which was defined as the time interval from picking up the device to the appearance of the first square waveform on capnography.”

“The insertion times of both devices were measured in a preliminary study (n = 12 for each), and average insertion times of the i-gel™ and LMA Supreme™ were 22.5 s (SD 8.1 s) and 32.7 s (SD 11.3 s), respectively. Sample size was calculated with an effect size of 1.032, power of 0.8, and \( \alpha \)-value of 0.05 (two-sided) and 16 patients were required per group. Taking into consideration a potential dropout rate of 15%, 19 patients were enrolled.”

The above sentences cite the case where the sample size calculation is appropriate in the published paper [8]. The primary outcome is clearly defined. Previous study data needed to calculate the effect size are presented, and the level of significance, power, and dropout rate are appropriately calculated.

Conclusion

For the sample size calculation, the following steps must be implemented consistently: 1) matching the primary outcome with the variable used to calculate the sample size; 2) presentation of appropriate significance, power, and effect size; and 3) application of the correct dropout rate. It is also necessary to resist the temptation to prove statistical significance by unnecessarily increasing the sample size. In addition to statistical significance, the clinical significance, cost-effectiveness, and ethical concerns regarding patients should be considered. When calculating the sample size, the appropriate dropout rate should be applied according to the characteristics of each study, and the sample size we want to obtain should be arrived at when the dropout rate is multiplied by the recruitment.

In reviewing the randomized controlled trials included in this study, only 20% (9/44) of the sample sizes were calculated. Many of the existing studies, including this paper, focused on the hypotheses and results of the study, but were relatively generous in power and sample size calculations. However, more and more journals require submissions based on the Consolidated Standards of Reporting Trials (CONSORT) checklist for systematic and transparent randomized control clinical studies, including the description of effect sizes. In order to properly conduct research, it is essential to understand the processes necessary to calculate the sample size, beyond the significance of the P value. Reviewers and editors should also carefully assess the appropriateness of the
sample size calculation process while evaluating the paper for publication in a journal.

Strict criteria for sample size are not a burden on the researcher. On the contrary, from the perspective of the researcher, strict criteria can save time and effort. It can help avoid the unfortunate situation where a paper produced after long and laborious work is not accepted due to issues related to sample size. In addition, from the journal’s point of view, it can help bring about a positive change. It can help change a culture in which only statistically significant results are published, and bring attention to interesting and useful studies having clinical significance, rather than exclusively statistical significance. Therefore, setting up a clear and strict system for sample size calculation, will make it possible to cultivate an environment in which studies with various results can be published without publication bias.

Conflicts of Interest

All authors are Statistical Round Board Members in KJA.

Author Contributions

Jae Hong Park (Writing – original draft)
Junyong In (Conceptualization; Writing – review & editing)
Hyun Kang (Methodology; Supervision)
Jong Hae Kim (Data curation)
Tae Kyun Kim (Data curation; Methodology)
Eun Jin Ahn (Data curation)
Dong Kyu Lee (Conceptualization; Data curation)
Sangseok Lee (Data curation; Methodology; Supervision)

ORCID

Junyong In, https://orcid.org/0000-0001-7403-4287

Hyun Kang, https://orcid.org/0000-0003-2844-5880
Jong Hae Kim, https://orcid.org/0000-0003-1222-0054
Tae Kyun Kim, https://orcid.org/0000-0002-4790-896X
Eun Jin Ahn, https://orcid.org/0000-0001-6321-5285
Dong Kyu Lee, https://orcid.org/0000-0002-4068-2363
Sangseok Lee, https://orcid.org/0000-0001-7023-3668

Jae Hong Park, https://orcid.org/0000-0003-0779-4483

References

Ultrasound-guided bilateral quadratus lumborum block vs. intrathecal morphine for postoperative analgesia after cesarean section: a randomized controlled trial

Eman Ramadan Salama

Department of Anesthesia and Surgical Intensive Care, Tanta University Faculty of Medicine, Tanta, Egypt

Background: Adequate pain control after cesarean section (CS) is crucial for mothers caring for newborns, and early ambulation to avoid thromboembolism and chronic abdominal and pelvic pain. This randomized controlled trial compared the efficacy of quadratus lumborum block (QLB) and intrathecal morphine (ITM) for analgesia after CS.

Methods: Ninety women at ≥ 37 weeks pregnancy scheduled for elective CS were enrolled. All patients received spinal anesthesia and post-operative QLB. They were randomly allocated to Control (anesthesia: 0.1 ml saline, QLB: 24 ml saline), ITM (anesthesia: 0.1 mg morphine, QLB: 24 ml saline), or QLB groups (anesthesia: 0.1 ml saline, QLB: 24 ml 0.375% ropivacaine). Integrated analgesia score (IAS) and numerical rating scale (NRS) scores at rest and during movement, morphine requirements in the first 48 h, time to first morphine dose and morphine-related side effects were recorded.

Results: IASs and NRS scores at rest and during movement were significantly lower in QLB and ITM group than in Control group. Moreover, IASs and NRS scores at rest and during movement were lower in QLB group than in ITM group. Time to first morphine dose was significantly longer in QLB group than in ITM and Control group. Further more, morphine requirements in the first 48 h were significantly lower in QLB group than in ITM group and Control group. Incidence of morphine-related side effects was significantly higher in ITM group than in QLB and Control group.

Conclusions: QLB and ITM are effective analgesic regimens after CS. However, QLB provides better long-lasting analgesia and reduced total postoperative morphine consumption.

Keywords: Analgesia; Cesarean section; Morphine; Quadratus lumborum; Spinal.

Introduction

Cesarean section (CS) is the most frequently performed surgical procedure in obstetrics and gynecology. It represents 27.2% of births in the most developed regions and 21.1% of those worldwide with a projection of further increase [1,2]. Adequate pain management after CS is vital to help new mothers feed and care for the newborn [3,4]. Furthermore, effective analgesia is crucial for early ambulation of parturients to avoid the risk of thromboembolism and development of chronic pain in the abdomen and pelvis [5].

Most CSs are performed under spinal anesthesia and opioids are still considered a cornerstone for postoperative analgesia that is systemic, spinal, or both [6,7]. However, it is
associated with undesirable side effects including delayed maternal respiratory depression, nausea, vomiting, and pruritis causing a reduction in overall patient satisfaction. Hence, alternative, opioid-free analgesic approaches are necessary [6,8].

Transversus abdominis plane (TAP) block is currently the most popular regional analgesic technique used for postoperative analgesia after CS. However, TAP block is inferior to intrathecal morphine (ITM) and of little benefit if used as a part of a multimodal regimen that includes ITM [6,8]. Acute pain after CS has both somatic and visceral components that result from surgical cutting of the abdominal wall and uterus. TAP block, as a part of a multimodal analgesic regimen after CS, provides effective analgesia for somatic pain at the abdominal wall [9].

Ultrasoundographic research into a new approach to TAP block has yielded the quadratus lumborum block (QLB). QLB was first reported at the annual European Society of Regional Anesthesia congress in 2007 (QLB I). In 2015, the QLB technique was modified by shifting the injection point from the anterolateral border of the quadratus lumborum to the posterior border (QLB II) [10]. QLB inhibits the dual pain components (somatic and visceral) as a result of local anesthetic spreading to the paravertebral space [9,10]. The analgesic efficacy of QLB II and its superiority over TAP block after CS were proved by Blanco [10,11]. The aim of this double-blind randomized controlled trial was to study the efficacy of QLB and ITM and compare the two treatment techniques for postoperative analgesia after CS.

Materials and Methods

After approval of the Research Ethical Committee of our hospital (Ethical Committee No. 31982/09/17) on 12 September 2017 and obtaining a written informed consent from all patients, 90 parturients were enrolled in this double-blind randomized placebo-controlled study between October 2017 and August 2018. The inclusion criteria were parturients with an American Society of Anesthesiologist physical status of II, those aged between 19 and 40 years, and scheduled for elective CS via a Pfannenstiel incision under spinal anesthesia. The exclusion criteria were a history of allergy to any of the study drugs, a body mass index (BMI) ≥ 35 kg/m², coagulopathy, local infection, pregnancy-induced hypertension, gestation diabetes mellitus, and opioid abuse. The study was registered at www.pactr.org (ID: PACTR201809600342881).

Based on numbers randomly generated by allocation software (QuickCalcs; GraphPad Software Inc., USA) in sealed opaque envelopes, parturients were allocated randomly into one of three groups: the Control group (n = 30), QLB group (n = 30), and ITM group (n = 30).

Oral ranitidine (150 mg) was administered to all patients at night and again 2 h before surgery. Before the patient was transferred to the operating room, an 18-gauge intravenous cannula was inserted into the nondominant arm or hand and 500 ml of hydroxyethyl starch (6% solution) was infused. In the operating room, standard monitoring was applied, including peripheral pulse oximetry, electrocardiography, and noninvasive arterial blood pressure.

Spinal anesthesia was performed under ultrasonographic guidance at levels of L2 to 3 or L3 to 4 intervertebral spaces, using a 27-gauge pencil point needle (Portex RapID™ Spinal Needle Set Pencil Point Spinal Needle, Smiths Medical International Ltd., UK) with 12.5 mg of hyperbaric bupivacaine 0.5% (AstraZeneca Pharmaceuticals, UK) and 10 µg of fentanyl (Martindale Pharmaceuticals, UK) combined with 0.1 mg of preservative-free morphine (0.1 ml) in the ITM group, and with 0.1 ml of 0.9% saline in the Control and the QLB groups. Subsequently, the parturients adopted the supine position with left uterine displacement of 15–20° and a facemask was applied to deliver oxygen at a rate of 6 L/min.

Five minutes after the spinal injection, the spinal anesthesia level was assessed by a pinprick and considered successful if a bilateral sensory blockade at T4–T6 was established. Anesthesia and surgical management were performed as per the hospital protocol.

After skin closure and the covering of the wound with a dressing, patients received intravenous paracetamol (1 g) and rectal diclofenac (100 mg). Ultrasound-guided QLB was then performed through the posterior approach, using the technique described by Blanco et al. [11], while the patients were still in the supine position and fully monitored.

A convex (5–8 MHz) ultrasound probe (SonoScape, China) with a protective sheath was used after imaging depth and gain was adjusted. The procedure was performed under complete aseptic conditions (including a facemask, gown, and gloves). After the abdominal skin was cleaned with an antiseptic solution, the probe was positioned transversely at the level of the anterosuperior iliac spine and then advanced in the cranial direction to visualize the three muscle layers of the abdominal wall. Following the external oblique muscle posterolaterally, its posterior border was identified (hook sign) with the internal oblique muscle below it displayed as a roof above the quadratus lumborum. The transducer was then tilted down to visualize the middle layer of the thora-columbar fascia as a bright hyperechoic line. A 21-gauge Stimuplex® A 100-mm needle (B. Braun Melsungen AG, Germany) was inserted in-plane under real-time ultrasound guidance in the anterolateral-to-posteromedial direction via the abdominal wall. Two milliliters of 0.9% saline was injected to visualize the solution.
spread (hydrodissection) to determine the optimal point of injection over the lumbar interfacial triangle. In the QLB group, 24 ml of 0.375% ropivacaine was then slowly injected on each side after negative aspiration in 4 ml aliquots (total dose, 180 mg), whereas in the Control and the ITM groups, patients received the same volume of 0.9% saline (placebo). Spread of the study solution was observed during the injection, revealing a tendency to diffuse post-teromedially rather than anterolaterally.

After the patients were transferred to the postanesthesia recovery unit, intravenous morphine was started via a patient-controlled analgesia (PCA) pump adjusted to deliver a bolus of 1 mg with a 5 min lockout period, a 4 h maximum dose of 48 mg, and no background infusion for the next 48 h (study period). The intensity of pain was assessed at rest and during movement (knee flexion) using the numerical rating scale (NRS) ranging from 0 to 10 (0 indicating no pain and 10 indicating severe intractable pain) at 2 h, 6 h, 12 h, 24 h, 36 h, and 48 h by nursing staff, and 1 g of paracetamol was administered intravenously if the NRS score was > 3, with a maximum dose of 4 g/24 h. All treating staff and outcome assessors were blinded to the study group allocation.

Patients were evaluated for their level of sedation using the Paseso Opioid-induced Sedation Scale [12], incidence of pruritus, and severity of postoperative nausea and vomiting (PONV), using a 4-point rating (4 = severe, 3 = moderate, 2 = mild, and 1 = absent), at 6 h, 12 h, 24 h, and 48 h. Patients were also monitored for respiratory depression, which was defined as a respiratory rate of ≤ 8 breaths/min. In addition, time to first postoperative morphine dose and time to first postoperative ambulation were recorded.

Intravenous ondansetron (4 mg) was administered to treat PONV and diphenhydramine (25 mg) was administered to treat pruritus. At the end of the study period, patients were asked to rate their satisfaction with the pain control regimen using a 3-point scale (1 = highly satisfied, 2 = satisfied, or 3 = dissatisfied).

The integrated analgesia score (IAS) was calculated at all NRS pain scores measurement time points using the following formula: (NRS + 1) × (1 + M / 10), where M indicates morphine dosage in milligrams 2 h before recording time of NRS. The basic formula of \[(PI \times [1 + M/10])\] [13], where PI is pain intensity, was modified by replacing PI with NRS + 1 to avoid a zero result when NRS = 0.

The primary outcome measure of this clinical study was the IAS at rest and during movement, and the secondary outcome measures were morphine consumption in the first 48 h, NRS pain scores at rest and during movement, time to first morphine dose, time to first ambulation, patient satisfaction, and morphine-related adverse effects including pruritus, nausea and vomiting, respiratory depression, and sedation.

Based on similar investigations [9,14], a sample size of 26 patients was calculated for an alpha error of 0.05, beta error of 0.1, probability (power) of 90%, and anticipated effect size of 0.40 using sample size software (G*Power Version 3.00.10, Franz Faul, Universität Kiel, Germany). Therefore, we included 30 patients per group to allow for any missing data or dropouts. Statistical analyses were performed using the Statistical Package for Social Sciences version 20 (SPSS Inc., USA). The Shapiro–Wilk test was first used to test the data for normality. Data were expressed as the mean ± SD, median (range), or frequency and percentage as appropriate. A one-way analysis of variance was used for analysis of normally distributed continuous data. The Kruskall–Wallis test was used for analysis of non-normally distributed continuous data. The chi-square test was used for pair-wise comparison of qualitative parameters among the groups after Bonferroni adjustment. A P value of < 0.05 was considered statistically significant.

Results

A total of 118 patients were eligible, among whom only 90 patients were enrolled in the study and randomized into three groups. No patient was excluded from the study thereafter because of deviation from the study protocol (Fig. 1). The three groups were comparable regarding the baseline maternity characteristics (Table 1). IASs and NRS scores at rest and during movement were significantly lower in the ITM and QLB groups than in the Control group at the various measurement time points. Moreover, the QLB group had lower IASs and NRS scores at rest and during movement in comparison to the ITM group (Figs. 2A, 2B, 3A, and 3B). Table 2 shows that time to first morphine dose was significantly longer in the ITM and QLB groups in comparison to the Control group at various measurement time points. Moreover, the QLB group had lower IASs and NRS scores at rest and during movement in comparison to the Control group (Table 2). The three groups were comparable regarding the time to first ambulation (P > 0.05) (Table 2). A significantly higher number of patients had pruritus in the ITM group than the Control and the QLB groups at 6 h. Moreover, the incidence of PONV was significantly higher in the QLB group than in the Control group at 12 h. Patient satisfaction with the assigned treatment regimen was significantly higher in the QLB group than in the Control and the ITM groups (Table 3). Sedation scale scores did not differ among the three groups, with no clinically detectable respiratory depression in any of the study patients (data not shown).
Fig. 1. CONSORT-flow diagram of participants in the study. ITM: intrathecal morphine, QLB: quadratus lumborum block.

Table 1. Maternity Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 30)</th>
<th>ITM group (n = 30)</th>
<th>QLB group (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32.5 ± 6.6</td>
<td>29.9 ± 7.5</td>
<td>31.1 ± 5.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.7 ± 11.3</td>
<td>78.9 ± 13.6</td>
<td>79.8 ± 12.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.7 ± 14.6</td>
<td>165.4 ± 15.6</td>
<td>164.7 ± 12.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.6 ± 6.7</td>
<td>28.5 ± 5.9</td>
<td>29.2 ± 6.2</td>
</tr>
<tr>
<td>Gestation age (weeks)</td>
<td>38.6 ± 1.4</td>
<td>39.2 ± 1.1</td>
<td>38.9 ± 1.8</td>
</tr>
<tr>
<td>Parity</td>
<td>1.5 ± 0.6</td>
<td>1.6 ± 0.6</td>
<td>1.6 ± 0.5</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD and were compared with Fisher’s exact test. ITM: intrathecal morphine, QLB: quadratus lumborum block, BMI: body mass index. No significant differences were seen among the three groups.

Table 2. Patient-controlled Analgesia Morphine Requirements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 30)</th>
<th>ITM group (n = 30)</th>
<th>QLB group (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine requirement (mg) at 48 h</td>
<td>61 ± 12.9</td>
<td>42.8 ± 10.4</td>
<td>18.2 ± 9.6</td>
<td>&lt; 0.05*</td>
</tr>
<tr>
<td>Time to first morphine dose (h)</td>
<td>2 (0.5–4)</td>
<td>8 (3–24)</td>
<td>17 (6–36)</td>
<td>&lt; 0.05'</td>
</tr>
<tr>
<td>Time to first ambulation (h)</td>
<td>11.7 ± 1.9</td>
<td>12.9 ± 1.6</td>
<td>13.4 ± 1.8</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or median (range). ITM: intrathecal morphine, QLB: quadratus lumborum block. *P values: ITM vs. Control = 0.001, QLB vs. Control = 0.001, QLB vs. ITM = 0.001. 'P values: ITM vs Control = 0.008, QLB vs. Control = 0.001, QLB vs. ITM = 0.002.
Discussion

Our results demonstrated that both QLB and ITM are effective postoperative analgesic regimens after CS; however, QLB provides longer-lasting analgesia with lower postoperative morphine requirements.

In our study, IASs and NRS scores were significantly lower in the ITM group for up to 12 and 6 h at rest and during movement, respectively, in comparison to the Control group. In addition, IASs and NRS scores during movement were significantly lower in the QLB group for up to 24 h in comparison to the Control and the ITM groups.

The overall benefits provided by any proposed analgesic technique may not be clearly identified when analgesic requirements and pain scores are used as isolated parameters [15]. Hence, we adopted the IAS described by Silverman et al. [13] as the primary outcome measure of the current study. The IAS provides a global end point based on a unique formula integrating pain intensity.

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Table 3. Morphine Related Side Effects and Patient Satisfaction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 30)</th>
<th>ITM group (n = 30)</th>
<th>QLB group (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>5 (16.7%)</td>
<td>12 (40%)</td>
<td>4 (13.3%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>12 h</td>
<td>6 (20%)</td>
<td>9 (30%)</td>
<td>7 (23.3%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>24 h</td>
<td>7 (23.3%)</td>
<td>6 (20%)</td>
<td>7 (23.3%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>48 h</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
<td>2 (6.7%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PONV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>absent</td>
<td>12</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>mild</td>
<td>14</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>severe</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12 h</td>
<td>absent</td>
<td>18</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>mild</td>
<td>10</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>2</td>
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<td>severe</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>24 h</td>
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<td>19</td>
<td>9</td>
<td>17</td>
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<td>8</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>1</td>
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<td>severe</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>48 h</td>
<td>absent</td>
<td>24</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
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<td>4</td>
<td>6</td>
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<tr>
<td></td>
<td>moderate</td>
<td>2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfaction</td>
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<td>11 (36.7%)</td>
<td>5 (16.7%)</td>
<td>28 (93.3%)</td>
</tr>
<tr>
<td></td>
<td>satisfied</td>
<td>14 (46.7%)</td>
<td>16 (53.3%)</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>dissatisfied</td>
<td>5 (16.6%)</td>
<td>9 (30%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or number only. ITM: intrathecal morphine, QLB: quadratus lumborum block, PONV: postoperative nausea and vomiting. *P values: ITM vs. Control = 0.045, QLB vs. Control = 0.602, QLB vs. ITM = 0.020, †P values: ITM vs. Control = 0.002, QLB vs. Control = 0.782, QLB vs. ITM = 0.001, ‡P values: ITM vs. Control = 0.172, QLB vs. Control = 0.001, QLB vs. ITM = 0.001.

and morphine consumption rather than a specific end point such as pain scores or analgesic requirements. We believe that the IAS improves sensitivity in assessing different treatment techniques. In our study, the IAS clarified the extended analgesic action of QLB during rest for up to 36 h, with a significantly lower IAS in comparison to the Control and the ITM groups. However, this was not noted when NRS scores were used as a pain intensity measurement tool at rest to compare QLB with ITM or placebos because NRS scores at rest were significantly lower in the QLB group in comparison to the Control and the ITM group until 24 h.

Our results also revealed that compared with the Control group, QLB provided an opioid-sparing effect of 70% during the first 48 h. By contrast, only a 30% reduction in morphine consumption was recorded in the ITM group. Furthermore, time to first morphine dose was significantly longer in the QLB group than in the ITM and the Control groups; it was also significantly longer in the ITM group than in the Control group.

ITM was previously the gold standard treatment for pain management after CS [16]. In a systemic review and meta-analysis, Mishriky et al. [17] found that ITM had greater analgesic efficacy in comparison to TAP block but was associated with a high incidence of morphine-related side effects. TAP block is an infiltration of local anesthetic solution in the anterior abdominal wall, as proved by Carney et al. [18] through magnetic resonance imaging of the chest and abdomen. In another systemic review and meta-analysis conducted by Champaneria et al. [19], TAP block was confirmed to have no additional benefits if combined with ITM. However, other studies found no differences between the two treatment techniques [16].

Our results are in concurrence with previous studies that have reported QLB as a successful postoperative pain control regimen after different types of surgery [20–23]. Moreover, our results are also in concurrence with those of Blanco et al. [10], who initially investigated QLB for pain control after CS by injecting 0.2 ml/kg of bupivacaine at 1.25 mg/ml on the posterior margin of the quadratus lumborum, resulting in a significant decrease in visual analogue pain scores and morphine consumption in the first 48 h. A year later, the same author group investigated QLB in comparison
to TAP block and proved that QLB had a significantly superior analgesic efficacy for up to 48 h [11]. However, to our knowledge, no previous studies have investigated and compared the analgesic efficacy of QLB and ITM for postoperative pain relief after CS.

QLB is a superficial posterior abdominal wall block that is technically easy to perform. It targets a very bright hyperechoic and easily dissected fascial plane. QLB level extends from T7 to T12 compared with T10 to T12 dermatomal distribution after TAP block [10]. This can be explained by two main theories: the spread of local anesthetic to the sympathetic nerve network in the thoracolumbar plane, and the spread of local anesthetic into the paravertebral space. These two theories can also explain the prolonged blockage effect and visceral pain control achieved by QLB but not by TAP block [11]. Hence, QLB is a safe, effective, and reliable analgesic option for postoperative pain control after abdominal surgeries [23–26].

In our study, compared with the other 2 groups, patients in the QLB group had no significant tendency for delay in ambulation. Weakness of the iliacus, quadriceps, and psoas muscles can result from the spread of local anesthetic after QLB, causing lumbar plexus block, as described by Wikner [27] in a case report.

Nausea, vomiting, pruritus, and respiratory depression are the major adverse effects of ITM. Nausea and vomiting are the most frequent adverse effects, occurring in approximately 30% of patients, whereas the incidence of pruritus ranges from 0% to 100% [28]. In our study, the incidence of pruritus was significantly higher in the ITM group at 6 h, whereas that of PONV was significantly higher in the ITM group at 12 h in comparison to the Control and the QLB groups, which led to the significantly lower number of patients who were satisfied with the treatment regimen in the ITM group compared to the QLB group.

In our study, sensory testing for evaluating block success was lacking because of efforts to preserve the blinding of group allocation. Obese patients with a BMI of ≥ 35 kg/m² were excluded from the study to ensure similar patient groups. Therefore, further investigation of QLB in this patient category is recommended to assess its efficacy. Furthermore, morphine might be used by the parturients through PCA pumps to control nonsurgical pain; however, they were instructed before starting the study to avoid the use of PCA pumps for such purposes. The optimal dose of local anesthetic in the case of QLB has not yet been determined and our study could not reveal any data about the ideal dose; hence, further research is warranted. The evaluation of pain scores and requirements of analgesia in pain control studies remains challenging. Hence, a combined outcome measure with improved validity was introduced in the form of the IAS, which is more consistent and informative. However, studying differences in treatment consequences still represents a major challenge and constitutes a limiting factor.

In conclusion, QLB and ITM are effective analgesic regimens after CS. However, QLB provides longer-lasting analgesia, reduced total postoperative morphine consumption, and improved patient satisfaction.

Conflicts of Interest

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

References


Background: The long-term outcomes of patients discharged from the hospital after successful care in the ICU in Korea are not briskly evaluated in Korea. The aim of this study was to assess long-term mortality of patients treated in the ICU and discharged alive from the hospital and to identify predictive factors of mortality.

Methods: In 3,679 adult patients discharged alive from the hospital after ICU care between 2006 and 2011, the 1-year mortality rate (primary outcome measure) was investigated. Various factors were entered into multivariate analysis to identify independent factors of 1-year mortality, including sex, age, severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II score), mechanical ventilation, malignancy, readmission, type of admission (emergency, elective surgery, and medical), and diagnostic category (trauma and non-trauma).

Results: The 1-year mortality rate was 13.4%. Risk factors that were associated with 1-year mortality included age (hazard ratio: 1.03 [95% CI, 1.02–1.04], P < 0.001), APACHE II score (1.03 [1.01–1.04], P < 0.001), mechanical ventilation (1.96 [1.60–2.41], P < 0.001), malignancy (2.31 [1.82–2.94], P < 0.001), readmission (1.65 [1.31–2.07], P < 0.001), emergency surgery (1.66 [1.18–2.34], P = 0.003), ICU admission due to medical causes (4.66 [3.68–5.91], P < 0.001), and non-traumatic diagnostic category (6.04 [1.50–24.38], P = 0.012).

Conclusions: The 1-year mortality rate was 13.4%. Old age, high APACHE II score, mechanical ventilation, malignancy, readmission, emergency surgery, ICU admission due to medical causes, and non-traumatic diagnostic category except metabolic/endocrinologic category were associated with 1-year mortality.

Keywords: Critical care outcomes; Intensive care unit; Long-term outcomes; Mortality; Risk factors; Survival analysis.
The starting point of long-term survival was defined as the date of discharge from hospital in order to determine the influence of ICU care for discharged patients after a full or partial recovery. Survival time was measured from the day of hospital discharge to December 1, 2012, using the National Health Insurance Service database. All patients were followed up for a minimum of 12 months and a maximum of 76 months. If patients were readmitted to the ICU during this period, only the data from their first admission were considered.

Statistical analysis

The demographic and clinical characteristics of patients were analyzed using the chi-squared test, independent t-tests, and the Mann-Whitney test. Continuous variables were expressed as mean ± standard deviation (SD). The ICU and hospital LOS, and APACHE II score did not follow a normal distribution. These were expressed as a median and interquartile range (IQR). The survival curve of total post-ICU patients was assessed using the

Materials and Methods

This single-center retrospective study was performed in the general ICU of an 805-bed university-affiliated hospital in Korea and was approved by the Institutional Review Board and Hospital Research Ethics Committee (November 12, 2012, protocol number 3-2012-0209). The ICU has 23 beds and admits about 965 patients per year. As a tertiary center, this general ICU treats almost all categories of critically ill patients, except neonates, open-heart, or neurosurgical patients. Patients who were admitted to the ICU between March 1, 2006, and November 30, 2011, were screened for the study. Among these patients, we selected those who had been discharged alive from the hospital and who were 20 years of age or older (Fig. 1). The following variables were collected using electronic medical records: sex, age, severity of illness at admission (Acute Physiology and Chronic Health Evaluation [APACHE] II score), mechanical ventilation, malignancy, readmission, ICU and hospital length of stay (LOS), type of admission (emergency, elective surgery, and medical), and diagnostic category (trauma and non-trauma such as cardiovascular, respiratory, gastrointestinal/hepatic, renal, neurologic, metabolic/endocrinologic, hematologic, septic shock, and transplantation). The severity of illness was estimated using the APACHE II score and recorded within 24 h of admission to the ICU. The types of admission were assigned at the time of each patient’s admission and recorded within 12 h of ICU admission.

Fig. 1. Flow diagram of patient screening for this study. The schematic shows the inclusion criteria for patients admitted to the ICU from 2006 to 2011. DNR: do not resuscitation, ICU: intensive care unit.
Kaplan–Meier analysis. Univariate and multivariate Cox’s post-intensive care unit (ICU) analyses were used to determine independent factors of 1-year mortality (primary outcome measure) and 5-year mortality (secondary outcome measure). Statistically significant variables (P < 0.05) on univariate analysis were included in a stepwise multivariate Cox’s proportional analysis. Statistical significance was defined as a P value of less than 0.05. Data were analyzed using IBM SPSS Statistics 20 (IBM Corp., USA) and SAS ver. 9.2 (SAS Institute Inc., USA).

Results
A total of 5,351 patients were admitted to the general ICU. Of these patients, 172 patients (younger than 20 years) and 673 patients (ICU readmission) were excluded from this study. A further 827 patients were excluded due to death in the hospital or a terminal prognosis. A total of 3,679 patients were finally included (Fig. 1). The demographic details and clinical characteristics of the participants are shown in Table 1. There were significant differences between post-ICU survivors and non-survivors based on age, APACHE II score, ICU LOS, hospital LOS, mechanical ventilation, malignancy, readmission, type of admission, and diagnostic category (P < 0.001).

The 1-year mortality rate was 13.4%, and a multivariate Cox’s proportional analysis showed that age (hazard ratio [HR] : 1.03 [95% CI, 1.02–1.04], P < 0.001), APACHE II score (1.03 [1.01–1.04], P < 0.001), mechanical ventilation (1.96 [1.60–2.41], P < 0.001), malignancy (2.31 [1.82–2.94], P < 0.001), readmission (1.65 [1.31–2.07], P < 0.001), emergency surgery (1.66 [1.18–2.34], P = 0.003), ICU admission due to medical causes (4.66 [3.68–5.91], P < 0.001), and non-traumatic diagnostic category (6.04 [1.50–24.38], P = 0.012) were independently associated with mortality (Table 2, Fig. 2).

As the subgroup analysis, we reviewed 831 patients admitted to ICU between 2006 and 2007 for the 5-year follow-up. The 5-year mortality rate was 35.5%, and age (1.04 [1.03–1.05], P < 0.001),

### Table 1. Demographic and Clinical Characteristics of Patients Admitted from March 1, 2006, to November 30, 2011

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n = 3,679)</th>
<th>Survivors (n = 3,186)</th>
<th>Non-survivors (n = 493)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>2154/1525</td>
<td>1873/1313</td>
<td>281/212</td>
<td>0.453</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60.0 ± 16.4</td>
<td>58.9 ± 16.5</td>
<td>67.0 ± 13.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>11.0 [7–16]</td>
<td>11.0 [7–15]</td>
<td>14 [9–19]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>2 [1–4]</td>
<td>2 [1–3]</td>
<td>3 [2–7]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>19 [12–32]</td>
<td>19 [12–31]</td>
<td>24 [14–41]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1454 (39.5)</td>
<td>1025 (37.8)</td>
<td>249 (50.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1290 (35.1)</td>
<td>1078 (33.8)</td>
<td>212 (43.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Readmission</td>
<td>402 (10.9)</td>
<td>307 (9.6)</td>
<td>95 (19.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Type of admission</td>
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<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Medical</td>
<td>1162</td>
<td>917 (90.3)</td>
<td>245 (9.3)</td>
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</tr>
<tr>
<td>Elective surgery</td>
<td>2047</td>
<td>1849 (89.4)</td>
<td>198 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>470</td>
<td>420 (78.9)</td>
<td>50 (21.1)</td>
<td></td>
</tr>
<tr>
<td>Diagnostic category</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Trauma</td>
<td>135</td>
<td>133 (98.5)</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>516</td>
<td>460 (89.1)</td>
<td>56 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>750</td>
<td>646 (86.1)</td>
<td>104 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal/hepatic</td>
<td>1099</td>
<td>922 (83.9)</td>
<td>177 (16.1)</td>
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<tr>
<td>Renal</td>
<td>130</td>
<td>104 (80.0)</td>
<td>26 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>723</td>
<td>639 (88.4)</td>
<td>84 (11.6)</td>
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</tr>
<tr>
<td>Metabolic/endocrinologic</td>
<td>96</td>
<td>88 (91.7)</td>
<td>8 (8.3)</td>
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<tr>
<td>Hematologic</td>
<td>23</td>
<td>17 (73.9)</td>
<td>6 (26.1)</td>
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<tr>
<td>Septic shock</td>
<td>160</td>
<td>138 (86.3)</td>
<td>22 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Transplantation</td>
<td>47</td>
<td>39 (83.0)</td>
<td>8 (17.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, median [IQR], number or patients or number (%). APACHE: Acute Physiology and Chronic Health Evaluation, ICU: intensive care unit, LOS: length of stay.

https://doi.org/10.4097/kja.d.18.00275
Table 2. Univariate and Multivariate Cox’s Proportional Analysis of Variables Associated with 1-year Mortality

<table>
<thead>
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<th>Parameter</th>
<th>Univariate (95% CI)</th>
<th>Multivariate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.03–1.04)</td>
<td>1.03 (1.02–1.04)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>1.05 (1.04–1.07)</td>
<td>1.03 (1.01–1.04)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1.62 (1.36–1.94)</td>
<td>1.96 (1.60–2.41)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.41 (1.18–1.69)</td>
<td>2.31 (1.82–2.94)</td>
</tr>
<tr>
<td>Readmission</td>
<td>2.09 (1.67–2.61)</td>
<td>1.65 (1.31–2.07)</td>
</tr>
<tr>
<td>Type of admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective surgery</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>1.12 (0.82–1.53)</td>
<td>1.66 (1.18–2.34)</td>
</tr>
<tr>
<td>Medical</td>
<td>2.37 (1.96–2.86)</td>
<td>4.66 (3.68–5.91)</td>
</tr>
<tr>
<td>Diagnostic category</td>
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<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>9.92 (2.48–39.78)</td>
<td>6.04 (1.50–24.38)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>7.71 (1.88–31.58)</td>
<td>6.17 (1.50–25.39)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9.88 (2.44–40.02)</td>
<td>5.31 (1.30–21.66)</td>
</tr>
<tr>
<td>Gastrointestinal/Hepatic</td>
<td>11.65 (2.89–46.95)</td>
<td>8.23 (2.02–33.52)</td>
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<tr>
<td>Renal</td>
<td>14.88 (3.53–62.68)</td>
<td>5.41 (1.27–23.01)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>8.23 (2.03–33.46)</td>
<td>5.63 (1.38–22.95)</td>
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<tr>
<td>Metabolic/Endocrinologic</td>
<td>5.74 (1.22–27.04)</td>
<td>3.31 (0.70–15.67)</td>
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<tr>
<td>Hematologic</td>
<td>20.41 (4.12–101.12)</td>
<td>8.87 (1.78–44.30)</td>
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<tr>
<td>Septic shock</td>
<td>9.92 (2.33–42.17)</td>
<td>4.34 (1.09–19.83)</td>
</tr>
<tr>
<td>Transplantation</td>
<td>12.59 (2.67–58.90)</td>
<td>18.15 (3.83–86.13)</td>
</tr>
</tbody>
</table>

Values are presented as numbers. APACHE: Acute Physiology and Chronic Health Evaluation, HR: hazard ratio.

Discussion

The observed 1- and 5-year mortality rates after hospital discharge in post-ICU patients were 13.4% and 35.5% respectively. The risk factors for 1-year mortality were age, APACHE II score, mechanical ventilation, malignancy, readmission, emergency surgery, ICU admission due to medical causes, and diagnostic category. The risk factors for 5-year mortality were age, mechanical ventilation, malignancy, readmission, ICU admission due to medical causes.

The predictors of long-term mortality have been previously reported [9,10]. In previous studies, the median value of 1-year mortality after critical care treatment in general ICU was 24% (5.4%–44%) [10–18]. These 1-year mortality rates were varied and the median mortality rate higher than our result (24% vs. 13.4%). One study reported 1-year mortality lower than our data.
(5.4% vs. 13.4%). In this Australian study [10], the starting point of follow-up was hospital discharge but they included patients who were 16 years and older. This difference can be attributed to the fact that some studies [10–18] started tracking mortality after ICU admission or discharge, while our study excluded deaths in the hospital when estimating mortality. The starting point of long-term follow-up is important when assessing mortality. Ranzani et al. [19] reported that if the starting point is changed “ICU admission” to “hospital discharge,” the mean difference is 25% and mean reduction is 54%. Using ICU admission as the starting point for follow-up includes in-ICU mortality. However, when hospital discharge is used as the starting point, the data included patients who are similar to patients with no ICU treatment and had better previous healthy condition. The good medical condition and status performance will influence the post-ICU survival (survivor bias) [19]. For intervention trials, the homogeneity of data should be needed. Ranzani et al. [19] recommended the ICU admission for the starting point because the long-term mortality is not limited to post-discharge mortality and ICU-acquired disease (e.g., ventilator-associated pneumonia, ICU-acquired myopathy, or delirium) should be included in mortality after critical care.

The major predictors of 1-year survival of patients discharged from the ICU were age, severity of disease (APACHE II score), mechanical ventilation, malignancy, readmission, type of admission, and diagnostic category. Many studies [9,10,13,20] have analyzed long-term mortality after ICU treatment, and the most common and most important factors that were associated with survival included age and severity of illness at the time of admission.

The age at ICU admission also appears to affect long-term survival, although age itself influences the death rate [10,20,21]. This factor was a strong predictor of the long-term survival of ICU patients (HR 1.03, P < 0.001).

The mortality rate for ICU patients after hospital discharge increased with the severity of illness. Any comorbidity before ICU admission, whether it was related to ICU admission or not, and the onset of malignancy also affected long-term survival rates [10,22]. Christiansen et al. [23] found that a high pre-admission morbidity level was related to short-term (30-day) and long-term (3-year) mortality rates. They also presented that morbidity had a greater impact on the mortality of ICU patients than that of a general population cohort. Thus, a chronic disease unrelated to the cause of ICU admission could affect the severity of illness and in-

https://doi.org/10.4097/kja.d.18.00275
crease long-term mortality even after the acute illness is treated.

We also found various mortality rates and HR between diagnostic categories. Similar to a previous study [11,16], the trauma group had the lowest HR, while the transplantation group had the highest HR. However, our study is not clearly comparable with others [6,10,11,13,16,24–26], as the diagnostic categories were not divided into uniform criteria. We suggest that subdivision of diagnostic categories or homogeneity of cases will be helpful for accurate analysis in future studies.

Long-term survival was also dependent on the type of admission. In this study, long-term survival was the lowest among patients who were admitted for a medical problem. Many studies [9,25–28] have shown various relationships between the type of admission and the long-term prognosis of patients after discharge. Medical patients are more likely to have pre-existing chronic diseases, which may be associated with mortality. Our result showed the 1-year mortality rates of emergency surgical patients were higher than that of elective surgical patients (Fig. 2). In the elective surgical group, included the patients admitted to the ICU for monitoring were included. The APACHE II score of all emergency surgical patients was statistically higher than that of elective surgical patients (emergency: 14.5 ± 7.7, elective: 12.3 ± 6.6, P < 0.001). This difference in severity of illness between the 2 groups might affect the mortality risk at 1 year after hospital discharge.

The 5-year mortality rate in our study was 35.5%, and this rate was similar to previous studies (29.4%–47.9%) [11,13,20,29–31]. Several other studies [10,11,13,20,25] have reported that the highest mortality rate was seen in the first year after ICU treatment, especially in the first 3 months. Meynaar et al. [20] found that the mortality rate in post-ICU patients decreased from 14.6% (first year) to 4.3% (sixth year), and the highest mortality rate was seen in the first 3 months (5.5%). In Western Australia [10], the mortality rate of hospital survivors was highest in the first 12 months (1 yr: 5.4%, 5 yr: 16.3%, 10 yr: 31.3%, 15 yr: 45.3%). We found that the mortality rate was highest in the first year after discharge, while the mortality rate gradually decreased.

The risk factors of 5-year mortality were age, mechanical ventilation, malignancy, readmission, and medical patients. There is a statistically significant difference in 1-year mortality analysis, but no difference in 5-year mortality analysis. In 2013, Brinkman et al. [9] performed the literature review of long-term mortality and Dutch cohort study; they showed a higher hazard ratio of urgent surgery than elective surgery at 3 months after hospital discharge and the risk decreased at 12 months after discharge. They explained this situation by the fact that patients who underwent urgent surgery have fewer comorbidities. In our study, the mortality risk factors at 5 years might be affected by the comorbidities (e.g., the percentage of patients with malignancy among emergency surgery group was 10.4% and elective surgery group was 55.3%). Furthermore, we excluded many patients who underwent cardiovascular surgery (e.g., coronary bypass, valve replacement, or aorta graft surgery) because they were admitted to a cardiac critical care unit instead of the general ICU. Neurosurgical patients, who were diagnosed with a brain tumor or hemorrhage and had frequent emergency surgery, were also excluded from this study in the same manner.

There are neither guidelines nor recommendations about management for improving long-term outcome while the studies about post-intensive care syndrome have been actively conducted. It is important to find the correctable factors for improving long-term mortality of post-ICU patients. The predictors in our study are difficult to modify by any interventions, such as age, severity of illness, malignancy, type of admission, or diagnosis, but the mechanical ventilation and readmission are correctable predictors. In the report from a stakeholder’ conference [32], they recommended some potentially available factors (e.g., pulmonary function, ICU-acquired weakness, cognitive impairment, depression, or posttraumatic stress disorder). Appropriate management of these correctable factors can be helpful in improving long-term outcome of post-ICU patients.

Even though this study was conducted with a large sample size in Korea, the analysis was still limited by several factors. First, data for chronic illnesses before ICU admission and cardiac arrest were not collected; therefore, the effects of these factors on ICU admission and mortality after discharge could not be investigated. Second, the ICU patient population in this study did not include patients undergoing open-heart or neurological surgeries, yet the number of patients presenting with neuromuscular complaints was particularly high. Third, we did not review the interventions performed in the ICU, such as renal replacement therapy or extracorporeal membrane oxygenation. Fourth, we did not evaluate the quality of life that has been widely reported as the important factors of long-term mortality, and we had not the data about the cause of out-hospital death. We are not able to know whether the cause of death is patient’s comorbidity or complication of critical care. Fifth, the readmission rate (10.9%) is extremely high. Although readmission related to the severity of illness, it also means that the ICU discharge was inappropriate. Finally, the purpose of this study was to investigate the factors affecting post-discharge mortality in ICU patients, but there is a limitation that we evaluate only factors known to be associated with hospitals or short-term mortality.

In conclusion, the 1-year mortality rate after hospital discharge in post-ICU patients was 13.4%. Risk factors that were associated
with 1-year mortality included old age, high APACHE II score, mechanical ventilation, malignancy, readmission, emergency surgery, ICU admission due to medical causes, and non-traumatic diagnostic categories except metabolic/ endocrinologic category.

Conflicts of Interest

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

Author Contributions

Se Hee Na (Formal analysis; Software; Writing – original draft; Writing – review & editing)
Cheung Soo Shin (Methodology; Supervision)
Kim Gwan Ho (Data curation; Investigation)
Jae Hoon Kim (Data curation)
Jong Seok Lee (Conceptualization; Writing – original draft; Writing – review & editing)

ORCID

Se Hee Na, https://orcid.org/0000-0003-4208-0769
Cheung Soo Shin, https://orcid.org/0000-0001-7829-8458
Gwan Ho Kim, https://orcid.org/0000-0002-3198-5039
Jae Hoon Kim, https://orcid.org/0000-0001-7134-7456
Jong Seok Lee, https://orcid.org/0000-0002-7945-2530

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Neuromuscular blockade reversal with sugammadex versus pyridostigmine/glycopyrrolate in laparoscopic cholecystectomy: a randomized trial of effects on postoperative gastrointestinal motility

Jihyun An, Heeyun Noh, Eunju Kim, Jihyang Lee, Kyeongyoon Woo, Hyunkyum Kim

Department of Anesthesiology and Pain Medicine, Daegu Fatima Hospital, Daegu, Korea

Background: Acetylcholinesterase inhibitors (e.g., pyridostigmine bromide) are used for neuromuscular blockade (NMB) reversal in patients undergoing surgery under general anesthesia (GA). Concurrent use of anticholinergic agents (e.g., glycopyrrolate) decreases cholinergic side effects but can impede bowel movements. Sugammadex has no cholinergic effects; its use modifies recovery of gastrointestinal (GI) motility following laparoscopic cholecystectomy compared to pyridostigmine/glycopyrrolate. This study evaluated the contribution of sugammadex to the recovery of GI motility compared with pyridostigmine and glycopyrrolate.

Methods: We conducted a prospective study of patients who underwent laparoscopic cholecystectomy. Patients were randomly allocated to the experimental group (sugammadex, Group S) or control group (pyridostigmine-glycopyrrolate, Group P). After anesthesia (propofol and rocuronium, and 2% sevoflurane), recovery was induced by injection of sugammadex or a pyridostigmine-glycopyrrolate mixture. As a primary outcome, patients recorded the time of their first passage of flatus (‘gas-out time’) and defecation. The secondary outcome was stool types.

Results: One-hundred and two patients participated (Group S [n = 49], Group P [n = 53]). Mean time from injection of NMB reversal agents to gas-out time was 15.03 (6.36–20.25) h in Group S and 20.85 (16.34–25.86) h in Group P (P = 0.001). Inter-group differences were significant. Time until the first defecation as well as types of stools was not significantly different.

Conclusions: Sugammadex after laparoscopic cholecystectomy under GA resulted in an earlier first postoperative passage of flatus compared with the use of a mixture of pyridostigmine and glycopyrrolate. These findings suggest that the use of sugammadex has positive effects on the recovery of GI motility.

Keywords: Cholinergic antagonists; Defecation; Flatulence; Gastrointestinal motility; Glycopyrrolate; Pyridostigmine bromide; Sugammadex.

Introduction

The use of acetylcholinesterases (e.g., rocuronium bromide) is essential in achieving neuromuscular blockade (NMB) for surgery under general anesthesia (GA), which requires a deep NMB [1]. For NMB reversal following the use of acetylcholinesterase, ace-
tylcholinesterase inhibitors (AChEIs)(e.g., neostigmine and pyridostigmine) are used as reversal agents. In addition, anticholinergic agents such as atropine and glycopyrrolate have been used to reduce the resulting cholinergic side effects, which include bradycardia and increased secretions [2,3].

Regarding bowel movements, AChEIs increase motility, whereas anticholinergic agents decrease it. Recovery to normal bowel movements and prevention of postoperative ileus are important for early recovery after surgery. One study reported that neostigmine, an AChEI, decreases postoperative ileus (a type of bowel obstruction) [4]. However, research comparing the effects of drugs with opposing effects on bowel movements has yet to be conducted.

Sugammadex, a recently introduced reversal agent, has no cholinergic side effects, and thus, it does not require the use of anticholinergic agents [3]. A number of studies have confirmed that the use of sugammadex for recovery from anesthesia leads to fewer respiratory complications and less residual NMB compared with the conventionally used AChEIs and anticholinergic agents, and that it contributes to enhanced recovery after surgery (ERAS®) [5,6]. ERAS® addresses the prevention of postoperative ileus as an important issue, for which investigations have been conducted to evaluate various preventive mechanisms, including gum chewing, early enteral nutrition, and laparoscopic surgery. In this context, few studies have been conducted to investigate the effects of sugammadex on bowel movements [7–10]. Moreover, only a small number of studies have compared the recovery of intestinal movement in groups administered AChEIs and anticholinergic agents and those administered sugammadex, although the studies were conducted retrospectively [11]. This study, therefore, aimed to evaluate the contribution of sugammadex as a reversal agent to the recovery of gastrointestinal (GI) motility in patients undergoing laparoscopic cholecystectomy compared to the contribution of the combination of pyridostigmine and glycopyrrolate.

Materials and Methods

This study was conducted with the approval of the Institutional Review Board (IRB) of Daegu Fatima Hospital (IRB approval number: DFH18MRIO366) and this study was registered at https://cris.nih.go.kr (KCT0004330). We explained to the patients the purpose of this prospective study and obtained their written consent before commencing the study.

We explained the method of anesthesia to the patients scheduled for laparoscopic cholecystectomy under GA as well as to their guardians. They were also informed concerning the use of NMB agents and the need for NMB reversal agents. We then explained to them the merits and demerits of the two types of reversal agents and obtained their consent to the randomized allocation of a drug.

Patient characteristics

We selected patients between ages 20 and 70 years who were scheduled for GA-induced laparoscopic cholecystectomy and had American Society of Anesthesiologists (ASA) physical status I or II.

Exclusion criteria

We excluded patients requiring emergency care due to their inability to control nothing by mouth (NPO) fasting time, and those diagnosed with diabetes, ulcerative colitis, or Crohn's disease, all of which can affect patient GI motility. Patients with renal dysfunction were also excluded [12,13].

Intervention

Fig. 1 shows the flow diagram of this study.

The study participants were allocated randomly to the experimental group, Group S (sugammadex), and the control group, Group P (pyridostigmine). Preoperatively, both groups fasted from midnight on the day of surgery and then consumed two cans of oral carbohydrate solutions (NONPO® 400 ml, Daesang Life Science, Korea) 4 h prior to surgery [8,9,14]. As premedication, midazolam 2 mg (IM) and famotidine 20 mg (IV) were administered 30 min before surgery. Upon arrival at the operation room, the patients were subjected to the induction of GA using propofol 2 mg/kg and rocuronium 0.6 mg/kg, both intravenously, while train-of-four (TOF) monitoring was in progress. Intubation proceeded with the confirmation of a TOF ratio of 0. To maintain GA, we used FiO₂ 0.5 and 2% sevoflurane (inhalational anesthetic) and injected a mixture of remifentanil 2 mg and normal saline 50 ml via infusion pump. For intraoperative fluid management, we avoided calcium ions, which can induce constipation. Instead, we used crystalloids (plasma solution A) intravenously at rates of 4 cc/kg/h for the first 10 kg, 2 cc/kg/h for the second 10 kg, and 1 cc/kg/h for every kg above 20 kg according to the 4-2-1 rule, and additional 1 cc/kg/h according to perioperative fluid management guidelines [15,16].

Following completion of surgery, administration of sevoflurane was stopped for recovery from GA. For NMB reversal, when a TOF of 2 or above was observed, we intravenously injected the patients with one of the two NMB reversal agents, i.e., sugammadex 2 mg/kg (Group S) or pyridostigmine 0.2 mg/kg and glycopyrro...
rrolate 0.008 mg/kg (Group P), and we recorded the time of injections. When the patients' TOF ratio was confirmed to have reached a minimum of 90%, we proceeded with extubation and transported the patients to the post-anesthesia care unit (PACU). Upon arrival in the PACU, palonosetron 0.075 mg was administered intravenously to prevent postoperative nausea and vomiting (PONV).

For pain control, we intravenously administered a mixture of propacetamol 2 g and normal saline 100 ml; in addition, as patient-controlled analgesia, instructions were provided for administration of normal saline 100 ml mixed with ketorolac tromethamine 240 mg. When patients complained of continued postoperative pain, with numerical rating scale of 6 or above, we provided additional pain control through intravenous administration of fentanyl 1 μg/kg (maximum of two injections). The amount of intraoperative remifentanil used was computed based on the amount of mixed fluid used recorded immediately after surgery.

After the patients were moved to their rooms, we intravenously administered tramadol PRN up to three times when pain intensity of 5 or above was indicated on the visual analogue scale. The patients maintained their NPO fasting throughout the day of the surgery.

Outcome

The patients were instructed to consume carbohydrate drink (NONPO® 400 ml, Daesang Life Science, Korea) on the morning of postoperative day (POD) 1 and to start with soft foods in the afternoon. To evaluate the patients' bowel movement recovery, following intake of food, they were instructed to record the time of their first passage of flatus ('gas out') in their rooms and the time of the first defecation to the minute. As a primary outcome, data on the time elapsed between the injection of NMB reversal agents and the first gas-out and defecation were collected and compared. As a secondary outcome, the presence of any adverse effect (such as nausea, vomiting, and dry mouth), as well as the types of stools additionally based on the Bristol stool scale (Fig. 2), were recorded for comparison.

Randomization

We employed simple randomization with a closed envelope technique for the allocation of the reversal agents. Two sealed envelopes were prepared, each containing a mark for Group S or Group P. Regarding patient assignments, neither the patients nor

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we were allowed to select or check the envelopes. Third parties with no involvement in the study selected the envelopes and then delivered them to other individuals (‘fourth parties’), who did not participate in the observation of the test results. The fourth parties were those who opened and checked the envelope contents. According to the allocations revealed, each drug (sugammadex vs. pyridostigmine and glycopyrrolate) was prepared to be administered as a reversal agent using 5 cc syringes and normal saline. Prepared in equal amounts, both agents were delivered back to the third parties and then administered randomly to the patients. The drug allocation chart was maintained by the fourth parties until the completion of data collection. It was not until delivery of the analyzed and compared results from the data from the fourth parties that we gained access to the details of the randomization. The patients and third parties were also denied access to the information up to that point.

Sample size

Power analysis was conducted using G*Power 3.1.9.4. Sample size of the previous study was based on the gas-out time in the general surgery ward [18]. Likewise, estimates of effective sizes were made using our previous record of cholecystectomy patients in the general surgery ward. An effect size of 0.527 was calculated using a mean gas-out time of 17 h with a standard deviation (SD) of 7.4 h in the sugammadex group and 20.6 h with a SD of 6.2 h in pyridostigmine group. A sample size of 48 patients per group was found to provide 80% power to detect the effect size with a set α of 0.05 for a two-sided design. A potential drop-out rate of 10% was taken into account. Finally, the study included a total 106 patients who underwent laparoscopic cholecystectomy.

Statistical analysis

We used Student’s t-test to analyze the height, weight, and age of the patients, the amount of remifentanil administered intraoperatively, and the amount of fentanyl administered in the PACU. Sex and ASA physical status classification (ASA scores) of the patients were examined with Fisher’s exact test. The Mann-Whitney U test was used for the analysis of gas-out and defecation times and Fisher’s exact test for stool type and analysis of data on adverse effects.

Results

A total of 106 patients were initially enrolled in the study. Of these, three patients were excluded owing to insufficient NMB reversal following administration of the reversal agent (experimental drug). In case of insufficient reversal, additional administration of sugammadex 2 mg/kg was performed. Another patient was excluded, as his surgery was changed intraoperatively from laparoscopic cholecystectomy to open surgery. As a result, 102 patients participated in the study (49 in Group S and 53 in Group P). The baseline characteristics of the patients were homogeneous (Table 1). Although the female participants in Group S outnumbered their male counterparts, the difference was not statistically significant. The two groups did not exhibit any significant differences in operation times, anesthesia times, amount of remifentanil adminis-
tered intraoperatively, or amount of fentanyl administered in the PACU (Table 1).

As a primary outcome, the time that elapsed between injection of the NMB reversal agent and the first gas-out was compared between the groups. Group S took 15.03 (6.36–20.25) h, and Group P took 20.85(16.34–25.86) h (P = 0.001) (Table 2). The sugammadex group took less time, and the difference was statistically significant.

Since cholecystectomy patients are usually discharged between POD 2 and POD 5, some of the study participants left the hospital before their first defecation time was recorded. We were able to check the defecation records of 28 of 49 patients in Group S and 28 of 53 patients in Group P. We found no significant difference between the groups (P = 0.694) (Table 2).

Group P took 47.26 (38.72–68.54) h, and Group S took 38 (25.07–64.74) h to achieve their first defecation (P = 0.087). Despite the shorter duration associated with Group S, the difference was not statistically significant (Table 2). Our analysis of stool types

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics and Perioperative Data</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
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<tr>
<td>Sex</td>
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<tr>
<td>M</td>
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<td>F</td>
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<td>Age (yr)</td>
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<td>ASA</td>
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<td>I</td>
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<tr>
<td>II</td>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Chronic cholecystitis</td>
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<tr>
<td>Gall bladder polyp</td>
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<tr>
<td>Gall bladder empyema</td>
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<tr>
<td>Operation time (min)</td>
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<tr>
<td>Anesthesia time (min)</td>
</tr>
<tr>
<td>Intraoperative remifentanil (ml)</td>
</tr>
<tr>
<td>PACU fentanyl (μg)</td>
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</tbody>
</table>

Values are presented as number (%) or mean ± SD. Group S: sugammadex group, Group P: pyridostigmine group. Student’s t-tests were performed, with values presented as mean ± SD. Chi-squared and Fisher’s exact tests were performed for sex and diagnosis, with values presented as number (%). ASA: American Society of Anesthesiologists physical status classification.

<table>
<thead>
<tr>
<th>Table 2. Comparison of Outcomes</th>
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<tbody>
<tr>
<td><strong>Group S (n = 49)</strong></td>
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<tr>
<td>Gas-out time (h)</td>
</tr>
<tr>
<td>Defecation (yes/no)</td>
</tr>
<tr>
<td>Defecation time (h)</td>
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<tr>
<td>Stool type according to Bristol stool chart</td>
</tr>
<tr>
<td>Type 1</td>
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<tr>
<td>Type 2</td>
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<tr>
<td>Type 3</td>
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<td>Type 4</td>
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<td>Type 5</td>
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<tr>
<td>Type 6</td>
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<tr>
<td>Type 7</td>
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</tbody>
</table>

Values are presented as median (interquartile range) or number (%). Group S: sugammadex group, Group P: pyridostigmine group. Statistical analyses were performed using the chi-squared and Fisher’s exact tests.
showed no significant differences between the groups (Table 2).
Differences in the incidence of adverse effects, namely nausea and vomiting, were also not significant. Dry mouth, on the contrary, was experienced by five patients in Group S, whereas 17 patients in Group P reported experiencing the same. This difference was found to be significant (Table 3).

**Discussion**

The findings of this study showed that sugammadex, used as a reversal agent in postoperative patients who underwent surgery under GA, resulted in a quicker recovery of patients’ GI motility compared to a pyridostigmine-glycopyrrolate mixture.

This result differs from previous studies. Sen et al. [18] were expected to improve bowel movements in patients undergoing thyroidectomy due to neostigmine. There was no difference in gas-out times between the sugammadex and neostigmine groups because of increased gastric emptying due to the affinity of steroid hormones for sugammadex. However, our study was based on the hypothesis that glycopyrrolate would predominate in terms of the effect on bowel movement when glycopyrrolate and pyridostigmine are injected simultaneously. The opposite action of pyridostigmine and glycopyrrolate may not be completely offset due to the difference in onset time and duration. Therefore, the use of sugammadex, which does not affect bowel movements, may have a positive effect on postoperative bowel movements compared to pyridostigmin/glycopyrrolate.

This finding is based on patients’ reports of their first postoperative passage of flatus. The finding can also be interpreted to represent a more natural postoperative recovery of GI motility, since the use of sugammadex does not affect patients’ bowel movements or peristalsis. However, we need to consider the conflicting effects on intestinal motility of the pyridostigmine-glycopyrrolate combination. In this regard, we may assume that the anticholinergic effects of glycopyrrolate on bowel movements can overcome the cholinergic side effects of pyridostigmine. One study has reported that neostigmine can promote GI motility in cases of postoperative ileus [19].

Another study found that AChEIs such as neostigmine and pyridostigmine are effective for acute colonic pseudo-obstruction and not ileus induced by mechanical bowel obstruction [20]. Both these studies indicate that AChEIs can increase bowel motility. Additionally, we found a previous study reporting that the concurrent use of neostigmine and atropine increased GI motility; however, the study design did not compare the drug mixture with any other agents. Furthermore, that study only investigated the impact on bowel movements based on the timing of atropine administration before neostigmine injection [21].

We acknowledge the slight differences between the published studies that we examined for our study. The duration of action associated with glycopyrrolate is 2–4 h, and that associated with pyridostigmine is longer than 2 h, which may lead to anticholinergic effects on bowel movements [22]. A number of previous studies have confirmed that the use of sugammadex for the reversal of NMB agents can lead to fewer incidents of respiratory complications, residual neuromuscular block, and PONV compared with the use of AChEIs [5,6]. The relevant literature also lists the advantages of the drug in terms of recovery of the cardiovascular system, urinary system, and other systems [23,24].

Based on the above findings, we may expect that sugammadex will have positive effects on the recovery of GI motility when used as an NMB reversal agent for patients who underwent surgery under GA and can help to decrease postoperative ileus. For prevention of postoperative ileus, a variety of approaches have been explored: gum chewing to induce a stimulatory effect; early mobilization that can reduce insulin resistance and have stimulatory effects; laparoscopic surgery that minimizes tissue trauma and bowel handling to reduce inflammatory reactions; use of non-steroidal anti-inflammatory drugs to reduce inflammatory reactions and opioid sparing; and early enteral nutrition and other similar regimens. Still, further benefits may be obtained with the use of comprehensive, multi-faceted approaches [10]. The use of sugammadex can be one such approach. Sugammadex is believed to enable faster postoperative nutrition and decrease GI complications such as constipation and postoperative ileus. These effects lead to reduced length of stay (LOS), which in turn contributes to ERAS® [25].

Notably, we did not find any significant inter-group differences

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**Table 3. Incidence of Adverse Effects**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Group S (n = 49)</th>
<th>Group P (n = 53)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>8 (16%)</td>
<td>8 (15%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
<td>0.708</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5 (8%)</td>
<td>17 (32%)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Values are presented as number (%). Group S: sugammadex group, Group P: pyridostigmine group. Statistical analyses were performed using the chi-squared and Fisher’s exact tests.
in terms of time elapsed until the first defecation reported by the patients. This is considered to be the limitation of our study due to the small number of samples. We attribute this lack of significant differences to the data loss caused by a relatively shorter LOS associated with laparoscopic cholecystectomy; a large number of patients left the hospital without reporting the first postoperative defecation within the LOS. This lost data resulted in a smaller sample size (n = 56) (Table 2). With a longer LOS and/or post-discharge phone interviews, we might have secured sufficient data on defecation times, which may have yielded statistically significant results. Inclusion of a larger sample of patients who remain committed to study participation until the time of their first postoperative defecation might have led to a significant difference in the types of stools.

Neostigmine (AChEIs) is known to increase the incidence of nausea and vomiting. However, its concurrent use with atropine or glycopyrrolate does not increase this incidence [26]. Controversial findings have been reported indicating that AChEIs can increase the risks of nausea and vomiting [27]. As indicated in the above research findings, differences in the incidence of nausea and vomiting were not statistically significant. Considering that the primary outcome of the study was not PONV, other risk factors (e.g., sex, smoking, and history of PONV) that could have been induced were not controlled by the study design. Hence, we see some difficulty in acknowledging the accuracy of the findings. Glycopyrrolate is associated with potent inhibition of salivary gland and respiratory secretions [28]. A significant difference in terms of dry mouth incidence was found in the pyridostigmine group.

The type of surgery targeted may also be a limitation of this study. Laparoscopic cholecystectomy, the focus of our study, involves less handling of the bowel and has fewer effects on bowel movements. Future studies should investigate other types of procedures, such as gastrointestinal surgery and colorectal surgery, which directly influence bowel movements due to the bowel handling and anastomosis involved. Using these surgical procedures, clearer outcomes may emerge in the recovery of GI motility in patients who undergo surgery under GA and are administered with the two reversal agents [29,30].

Furthermore, measuring gastrointestinal transit time by using a scintigraphic method with radioisotopes attached to drugs will likely enable a more accurate comparison of sugammadex against conventional reversal agents.

In conclusion, for patients undergoing laparoscopic cholecystectomy surgery under GA, the use of sugammadex as an NMB reversal agent resulted in an earlier first postoperative passage of flatus compared with the use of a mixture of pyridostigmine and glycopyrrolate. These findings suggest that the use of sugammadex has positive effects on the recovery of postoperative GI motility.

**Conflicts of Interest**

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

**Author Contributions**

Heeyun Noh (Conceptualization; Data curation; Investigation; Methodology; Resources; Writing – original draft; Writing – review & editing)
Jihyun An (Conceptualization; Formal analysis; Methodology; Supervision)
Eunju Kim (Methodology; Project administration; Software)
Jihyang Lee (Conceptualization; Supervision; Validation; Writing – review & editing)
Kyeongyoon Woo (Data curation; Formal analysis; Project administration; Visualization)
Hyunkyum Kim (Data curation; Investigation; Resources)

**ORCID**

Jihyun An, https://orcid.org/0000-0002-5373-3887
Heeyun Noh, https://orcid.org/0000-0001-5301-8675
Eunju Kim, https://orcid.org/0000-0002-7299-4644
Jihyang Lee, https://orcid.org/0000-0001-5038-8419
Kyeongyoon Woo, https://orcid.org/0000-0002-5130-8721
Hyunkyum Kim, https://orcid.org/0000-0002-4539-8257

**References**


Background: Catheter-related bladder discomfort (CRBD) is a frequent complaint after awakening from anesthesia in patients receiving perioperative bladder catheterization. Overactive bladder (OAB) and CRBD show similar symptoms; thus, drugs used for the management of OAB influence symptoms of CRBD. Trospium chloride has been found effective in managing resistant cases of OAB. We evaluated the efficacy of oral trospium on CRBD in the postoperative period.

Methods: Sixty-four male and female adult patients, with planned spinal surgery and requiring urinary bladder catheterization, were randomly divided into two groups of 32 each. Group T patients received 60 mg extended-release oral trospium (extended-release) 1 h before induction of anesthesia and Group C patients received a similar-looking placebo. The anesthetic technique was identical in both groups. The CRBD score was evaluated in the postoperative ward using a 4-point scale (1 = no discomfort, 2 = mild, 3 = moderate, 4 = severe). Readings were recorded on arrival (0 h), and 1 h, 2 h, and 6 h postoperatively. All patients received fentanyl for postoperative pain relief.

Results: The incidence of CRBD was significantly higher in Group C than in Group T at 0 h (66% vs. 22%, P = 0.001) and 1 h postoperatively (72% vs. 28%, P = 0.001). The incidence of moderate to severe CRBD was higher in Group C at postoperative 2 h (82% vs. 14%, P = 0.004). There was no significant difference in postoperative fentanyl requirements.

Conclusions: Pretreatment with 60 mg extended release trospium reduced the incidence and severity of CRBD in the early postoperative period.

Keywords: Antimuscarinic Muscarinic antagonists; Muscarinic receptors; Overactive bladder; Postoperative period; Trospium chloride; Urinary catheterization.

Introduction

The salient features of catheter-related bladder discomfort (CRBD) are urinary urgency, frequency with or without urge, and incontinence observed after bladder catheterization [1]. The presence of a urinary catheter may be distressing to the patient and manifests as agitation, restlessness, or pulling out of the catheter. The clinical presentations of overactive bladder (OAB) and CRBD are quite similar, and thus drugs useful in managing OAB could be used in the prevention of CRBD [2,3]. Antimuscarinic agents are the first choice of drugs for OAB [4]. Darifenacin and solifenacin have recently been studied for the prevention of CRBD with varying success rates [5]. Other groups of drugs, such as...
antiepileptics (gabapentin and pregabalin) [6,7], ketamine [8], tramadol [9], and dexmedetomidine [10], have shown varying degrees of success for prevention of CRBD.

Trospium chloride [11] is a non-selective muscarinic receptor antagonist and a quaternary ammonium compound found to be effective in treating resistant cases of OAB [12,13]. This study was designed to evaluate the effectiveness of trospium chloride for the prevention of CRBD in patients undergoing spinal surgery and requiring catheterization.

Materials and Methods

After approval from the Institutional Ethical Committee (AHB/CR/95/26-07-2016) and written informed consent from patients, this study was performed on 74 patients with American Society of Anesthesiologists physical status I and II of either sex, aged 20–65 years, who were undergoing elective spinal surgery and required catheterization of the urinary bladder. This study was registered at ClinicalTrials.gov [www.clinicaltrials.gov, ref: CTRI/2016/11/007423]. Exclusion criteria were known sensitivities to study drugs, bladder outflow obstruction, overactive bladder, preoperative neurological bladder/bowel involvement, chronic pain, drug or alcohol abuse, and cardiovascular or hepatic disease. Eligible patients were randomly distributed into two groups, with the help of a computer-generated table of random numbers. Group T (trospium) received 60 mg of extended release (ER) oral trospium 1 h prior to induction of anesthesia with sips of water. Group C (control) received an oral placebo tablet 1 h prior to induction of anesthesia with sips of water.

In similar-looking envelopes marked T and C, the study drugs were given to the anesthesia registrar who administered the drugs as per instructions with sips of water. In the operating room, after establishing monitoring systems (electrocardiography, pulse oximetry, and noninvasive blood pressure), the patients in both groups received injections of midazolam (0.03 mg/kg), fentanyl (1.5 μg/kg), and propofol (1.5–2.0 mg/kg), followed by vecuronium (0.1 mg/kg) for muscle relaxation. Tracheal intubation was completed with an appropriate-sized cuffed endotracheal tube. Anesthesia was maintained with oxygen:nitrous oxide (O2:N2O at a ratio of 33:66), sevoflurane, and intermittent boluses of vecuronium and fentanyl as required. Urinary catheterization was performed under strict aseptic precautions with a 16F Foley catheter after lubricating the urethra with water-soluble lubricating jelly (Neon Laboratories, India) and 10 ml of normal saline was used to inflate its balloon. Catheter fixation was done in the suprapubic region without traction. Perioperative inadequate analgesia was defined as an increase in mean arterial pressure > 20% or heart rate > 30% from baseline in response to a surgical stimulus. In these situations, an intravenous bolus of fentanyl (0.5 μg/kg) was administered. At the end of surgery, the neuromuscular blockade was reversed with neostigmine (40 μg/kg) and glycopyrrolate (10 μg/kg), the trachea was extubated, and patients were moved to the post-anesthesia care unit (PACU). All patients received postoperative analgesia with fentanyl (5 μg/ml) through a patient-controlled analgesia pump (Smiths Medical, USA) in the PACU. Fentanyl requirements in the first 6 hours postoperatively were recorded.

Primary outcome

The primary outcome of this study was the incidence and severity of CRBD, which was recorded on a 4-point severity scale [8] (1 = no discomfort; 2 = mild, admitted on questioning only; 3 = moderate, told by the patient without being questioned; 4 = severe, urinary urgency demonstrated by behavioral changes such as attempts to remove the catheter, verbal responses, and restless movements of extremities) on arrival (0 hour) and again at 1, 2, and 6 hours (h) postoperatively.

Secondary outcome

The secondary outcomes included perioperative fentanyl requirements and side effects of the study drug (such as dry mouth, facial flushing, blurred vision, constipation, agitation, or tachycardia).

Sample size calculation

The sample size was calculated by employing a two-sided P level. The reported incidence of CRBD in our previous study, secondary to intraoperative catheterization, was 70% in spinal surgery at 0 h (primary endpoint) [7]. Assuming that the CRBD incidence in Group C was equal to that of the previous study and the CRBD incidence in Group T was set as 30% (with α = 0.05 and β = 0.80) based on a pilot study, the effect size used was 0.8 based on these proportions (Cohen’s $h = 2 \times \arcsin \sqrt{p_1} - 2 \times \arcsin \sqrt{p_2} = 0.82$), [14] which resulted in a sample of 25 patients per group to attain the desired effect. Considering a 25% drop-out rate, a sample of 32 patients in each group was targeted.

Statistical analysis

Statistical analysis was done using the statistical software Prism (version 7.0; GraphPad Software, USA). The normality of data was assessed by the Kolmogorov-Smirnov test. Student t-test was
used for continuous variables and Pearson’s chi-squared test was used for categorical variables. Fisher’s exact test was used to analyze the incidence and severity of bladder discomfort (mild, moderate, and severe) and the incidence of side effects. An alpha value adjustment with Bonferroni’s correction (i.e., the alpha value divided by the number of comparisons) was performed to compare the incidence and severity of CRBD between the two groups at each time point. A P value of < 0.05 was considered statistically significant.

**Results**

A total of 74 patients were assessed for eligibility, out of which 64 patients were studied after randomization and all patients completed the study (Fig. 1). Ten patients were eliminated from the study due to the preoperative use of pregabalin and analgesics (paracetamol, flupertine, and tramadol). There were no significant differences between patient demographics ($P = 0.750$), surgery duration ($P = 0.627$), or intraoperative fentanyl ($P = 0.627$) requirement between the groups (Table 1).

The incidence of CRBD was 66% in Group C (22% in those < 50 yr and 44% in those > 50 yr) and 22% in Group T (6% in those < 50 yr and 16% in those > 50 yr) at 0 h. The overall incidence of CRBD in Group C was significantly higher than in Group T at 0 and 1 h postoperatively. In the subgroup analysis according to age, the incidence of CRBD in Group C was significantly higher than in Group T at all time intervals in the > 50 age group ($P = 0.004$ at 0 h, $P = 0.007$ at 1 h, $P = 0.008$ at 2 h, and $P = 0.003$ at 6 h), but the incidence of CRBD was not significant between the two groups in the < 50 age group.

CRBD severity (mild vs. moderate to severe) was significantly decreased in Group T compared to Group C at 2 h postoperatively ($P = 0.004$). In the subgroup analysis according to age, CRBD severity (mild vs. moderate to severe) was significantly decreased in group T compared to Group C at 1 h ($P = 0.006$) and 2 h ($P = 0.011$) postoperatively in the > 50 age group, while at other time intervals the severity was not significant between these two groups. The majority of patients in Group T had only mild discomfort (Table 2). The absolute risk reduction with trospium was 44%, the relative risk reduction was 61%, and the number needed to treat was 2.

There were no significant differences in postoperative fentanyl requirements between Group C ($342.7 \pm 51.8 \mu g$) and T ($352.3 \pm 66.4 \mu g$) within 6 h postoperatively ($P > 0.05$). The use of trospium was associated with a higher incidence of dry mouth (15%) compared to the control group (9%). There were no significant differences between the two groups in other side effects (Table 3).

**Table 1. Demographic and Clinical Profile of Study Participants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group C (n = 32)</th>
<th>Group T (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.6 ± 7.8</td>
<td>52.8 ± 6.1</td>
<td>0.065</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>25/7</td>
<td>23/9</td>
<td>0.773</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.6 ± 8.3</td>
<td>63.7 ± 9.9</td>
<td>0.362</td>
</tr>
<tr>
<td>Spine surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical/lumbar</td>
<td>10/22</td>
<td>12/20</td>
<td>0.793</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>148.9 ± 32.6</td>
<td>145.0 ± 36.9</td>
<td>0.655</td>
</tr>
<tr>
<td>Intra-operative fentanyl requirement (μg)</td>
<td>118.6 ± 18.3</td>
<td>123.7 ± 20.7</td>
<td>0.296</td>
</tr>
<tr>
<td>Post-operative fentanyl requirement (μg)</td>
<td>342.7 ± 51.8</td>
<td>352.3 ± 66.4</td>
<td>0.518</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number. Group C: control group, Group T: trospium group.
Table 2. Incidence and Severity of Catheter-related Bladder Discomfort

<table>
<thead>
<tr>
<th>Postoperation (h)</th>
<th>0 h</th>
<th>1 h</th>
<th>2 h</th>
<th>6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group C (n = 32)</td>
<td>Group T (n = 32)</td>
<td>Group C (n = 32)</td>
<td>Group T (n = 32)</td>
</tr>
<tr>
<td>Bladder discomfort</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>11 (34)</td>
<td>9 (28)</td>
<td>21 (66)</td>
<td>23 (72)</td>
</tr>
<tr>
<td>P value (incidence)</td>
<td>0.001*</td>
<td>0.019</td>
<td>0.001*</td>
<td>0.016</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.33 (0.16–0.67)</td>
<td>0.39 (0.22–0.71)</td>
<td>0.41 (0.19–0.85)</td>
<td>0.25 (0.07–0.8)</td>
</tr>
</tbody>
</table>

Grading of discomfort

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate to severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (29)</td>
<td>15 (71)</td>
</tr>
<tr>
<td>4 (57)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>5 (22)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>6 (67)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>3 (18)</td>
<td>14 (82)</td>
</tr>
<tr>
<td>6 (86)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>5 (42)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>2 (67)</td>
<td>1 (33)</td>
</tr>
</tbody>
</table>

P value (severity) 0.207 0.035 0.004* 0.569

Values are presented as the number of patients (%). Group C: control group, Group T: trospium group. P values are calculated using Pearson's chi-squared test. *Presents statistical significance adjusted for multiple comparisons applying Bonferroni's correction at P = 0.0125.

Table 3. Incidence of Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Group C (n = 32)</th>
<th>Group T (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative nausea and vomiting</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Facial flushing</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (9)</td>
<td>5 (15)</td>
<td>0.707</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number of patients (%). Group C: control group, Group T: trospium group.

Discussion

CRBD as a postoperative phenomenon is associated with emergence agitation, increased analgesic requirements, and sometimes behavioral changes, and needs active management. The incidence of CRBD varies between 40% and 80% among different surgeries with a maximum incidence reported in genitourinary surgeries [15]. Sometimes it is difficult to differentiate CRBD from spasms or pain associated with genitourinary surgeries. Therefore, we selected spinal surgeries for our study. Other factors influencing the incidence of CRBD are sex (male), catheter diameter [16], and perioperative medications (pregabalin, dexametomidine, paracetamol) [7,10,17]. In recent studies, the use of glycopyrrolate as a premedication or part of reversal agents for antagonizing the neuromuscular blockade have been found to influence the incidence of CRBD [18,19]. We did not specifically study this aspect; however, their effect cannot be denied as the incidence of CRBD in our study was 66% (control group) at 0 h, which was similar to other studies. The use of trospium further decreased the incidence of CRBD. The use of sevoflurane has also been shown to decrease the incidence of early CRBD compared to desflurane and propofol [20,21]. It has been postulated that the effect of sevoflurane is short-lived (up to one hour postoperatively) due to its effect on M3 receptors.

There are 5 muscarinic receptor subtypes (M1-M5) present in the human body, each of which have different functions [22]. M2 receptors (70–80%) are the predominant cholinceptors present in the urinary bladder, while M3 receptors (20–30%) in the bladder mediate detrusor contraction. Hence, selective M2 and M3 receptor antagonists have a therapeutic role in the prevention of CRBD without producing the systemic side effects of anticholinergic drugs. Trospium has a greater affinity for M2 and M3 muscarinic receptors than other muscarinic receptor subtypes.

The mechanism of antimuscarinic agents for the prevention of CRBD is through a reduction of detrusor overactivity by decreasing both contraction frequency and intensity [23]. Additionally, they inhibit bladder afferent mechanisms during the filling phase and increase bladder capacity. Because of these effects, antimuscarinic agents have become a mainstay of treatment for CRBD. Trospium has shown higher tissue selectivity in inhibiting detrusor contraction over salivation, offering an advantage over other agents by reducing detrimental effects and improving compliance. Older antimuscarinic agents, like oxybutynin and tolterodine, have no specificity for any subtype [2].

We administered 60 mg ER trospium, as this is the most effective single daily dose in an overactive bladder [24]. In our institute, most elective spinal surgeries take 2–2.5 h. If anesthesia time is added, then the patients arrive at the PACU after 2.5–3 h. Peak plasma levels of trospium are achieved within 4–5 h. Therefore, trospium administration 1 h before induction roughly corresponded to the peak effect of trospium. The elimination half-life

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of tropium is 10–20 h; therefore, we expected its effect for 12 h postoperatively. In our study, the peak effect of tropium occurs 0–2 h postoperatively, which is why the significant decrease in the incidence and severity of CRBD in our study occurred during this period only. However, we did not assess the CRBD score beyond 6 h due to our study protocol.

Agarwal and colleagues observed that oxybutynin and tolterodine decreased the CRBD incidence by 20–25% [25]. We found a 43% decrease in the CRBD incidence with the use of tropium. Tauzin-Fin et al. [26] also demonstrated that a reduction in the incidence of CRBD was about 48% with 5 mg oxybutynin sublingually. However, the results of this study may have been affected by the use of gabapentin as premedication and tramadol at the timing of wound closure. Both of these drugs also decrease the incidence of CRBD; therefore, this study basically used a cocktail regimen. We also observed a significant decrease in the incidence of dry mouth (15%) and other adverse effects in the tropium group compared with previous studies [25,26] on oxybutynin and tolterodine (P < 0.05).

There are certain limitations to this study. It was not possible to analyze the difference in CRBD score with respect to the different doses or a minimally effective dose due to the fixed dose of the drug in this study. Research on the effectiveness of different dosages of tropium, durations of more than 6 h, and their effect by patient sex to decrease the incidence and severity of CRBD score needs further investigation.

In conclusion, 60 mg of ER tropium administered 1 h prior to induction of anesthesia significantly decreased the incidence and severity of CRBD in the early postoperative period, but at the cost of a marginally increased incidence of dry mouth.

Conflicts of Interest

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

Author Contributions

Vinit Kumar Srivastava (Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Software; Supervision; Visualization; Writing – original draft; Writing – review & editing)
Sanjay Agrawal (Conceptualization; Methodology; Resources; Supervision; Writing – original draft; Writing – review & editing)
Sweta Anil Deshmukh (Conceptualization; Methodology; Resources; Software; Supervision; Writing – original draft)
Febin Noushad (Methodology; Resources; Software; Visualization)
Saima Khan (Conceptualization; Formal analysis; Investigation; Methodology; Resources)
Raj Kumar (Conceptualization; Methodology; Resources; Supervision; Writing – original draft)

ORCID

Vinit Kumar Srivastava, https://orcid.org/0000-0002-8430-7290
Sanjay Agrawal, https://orcid.org/0000-0002-2806-1943
Sweta Anil Deshmukh, https://orcid.org/0000-0002-5269-8776
Febin Noushad, https://orcid.org/0000-0002-4297-0852
Saima Khan, https://orcid.org/0000-0001-9139-9093
Raj Kumar, https://orcid.org/0000-0002-4896-5229

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18. Kim JH, Lee HS, Jo HR, Je UJ, Paek JH. Effects of glycopyrrolate premedication on preventing postoperative cathe-
Effect of BMS-470539 on lipopolysaccharide-induced neutrophil activation

Seongheon Lee1*, Wan Ju1*, Tran Duc Tin2, Joungmin Kim1, Jeong Seok Lee3, Cheon Hee Park3, Sang Hyun Kwak1,2

1Department of Anesthesiology and Pain Medicine, Chonnam National University Medical School & Hospital, 2Brain Korea 21 Project, Center for Creative Biomedical Scientists at Chonnam National University, 3Department of Anesthesiology and Pain Medicine, Gwangju Christian Hospital, Gwangju, Korea

Background: BMS-470539, a recently introduced selective agonist of the melanocortin 1 receptor, is known to have anti-inflammatory properties. In this study, we investigated the effects of BMS-470539 on lipopolysaccharide (LPS)-induced inflammatory responses and delayed apoptosis with its signaling pathways in human neutrophils.

Methods: Isolated human neutrophils were incubated with various concentrations of BMS-470539 (1, 10, and 100 µM) in the presence or absence of LPS (100 ng/ml), and the expression of pro-inflammatory cytokines, such as tumor necrosis factor alpha, interleukin (IL)-6, and IL-1β, were assessed. The effects of BMS-470539 on the expression of mitogen-activated protein kinases (MAPKs), such as p38, extracellular-signal-regulated kinase 1/2, and c-Jun N-terminal kinase, and the expression of nuclear factor kappa B (NF-κB) in LPS-stimulated human neutrophils, were evaluated by enzyme-linked immunosorbent assay. Neutrophil apoptosis was also measured by fluorescence-activated cell sorting (annexin V/propidium iodide) in LPS-stimulated neutrophils under treatment with BMS-470539.

Results: BMS-470539 attenuated LPS-induced expression of pro-inflammatory cytokines, and phosphorylation of MAPKs and NF-κB. LPS stimulation reduced neutrophil apoptosis compared to the controls; however, BMS-470539 significantly inhibited the reduction of neutrophil apoptosis.

Conclusions: BMS-470539 can suppress the inflammatory responses of LPS-stimulated neutrophils by inhibition of MAPK pathways or NF-κB pathway, and it can also inhibit LPS-delayed neutrophil apoptosis.

Keywords: Apoptosis; BMS-470539; Cytokines; Lipopolysaccharides; Mitogen-activated protein kinases; Neutrophils; nuclear factor-kappa B.

Introduction

Neutrophils are the first cells to join the immune defense system of the body to protect against invading pathogens [1]. Under non-infectious conditions, neutrophils are functionally quiescent with short lifespans of 6–12 h, and the number of neutrophils is kept constant through apoptosis. When neutrophils become activated under infectious conditions, the functionality of neutrophils markedly increases with prolonged survival. This process is advantageous in most infectious conditions. However, massive and uncontrolled secretion of pro-inflammatory cytokines may cause host tissue injury in an excessive inflammatory condition, such as severe sepsis [2].
The melanocortin 1 receptor (MC1R) is a G protein-coupled receptor involved in normal pigmentation of skin and hair. MC1Rs are primarily located on the surface of melanocytes, which produce a pigment called melanin. MC1Rs have been also detected on various immune cells other than melanocyte, including neutrophils, monocytes, and dendritic cells [3–5]. Although the active functions of MC1R in immune cells, especially for neutrophils, have not been previously elucidated in detail, including the signaling pathway and impact on cell survival, some preclinical investigations indicate activation of MC1R could be a new strategy to control inflammatory disorders with a collective reduction of the major molecules involved in the inflammatory process. Therefore, a selective agonist of MC1R has emerged as a promising candidate for down-regulating the excessive inflammatory condition, and the development of the ideal drug with receptor selectivity according to the intended indication has been desired.

The compound BMS-470539 is a recently synthesized small-molecule agonist of human and murine MC1R, and a few studies have assessed the roles of this compound until now. BMS-470539 is highly selective to MC1R, with weak or no activity at other subtypes of melanocortin receptors [6]. In addition to selectivity, BMS-470539 has favorable pharmacokinetic properties, with a prolonged half-life relative to the nonselective melanocortin, Nle-1-D-Phe²-MSH (1.7 h vs. 20 min) [7]. BMS-470539 was reported to inhibit pro-inflammatory cytokine accumulation and leukocyte infiltration and adhesion in mice [8,9]. Through these in vivo studies, however, it is not clear which cells are directly involved in mediating the anti-inflammatory action of BMS-470539.

The purpose of the present study was to investigate the anti-inflammatory effect of BMS-470539 on lipopolysaccharide (LPS)-stimulated human neutrophils with its intracellular signaling pathway, and to investigate whether BMS-470539 modulates apoptosis of LPS-stimulated human neutrophils.

Materials and Methods

For isolation of neutrophils, the peripheral blood of healthy volunteers was used under a protocol approved by the Chonnam National University Hospital Institutional Review Board (IRB no. CNUH-2012-048) and written informed consent was obtained from all volunteers. Dextran (6%) was added and erythrocytes were sedimented under gravity for 45 min at room temperature. Then leukocyte-enriched pellets were collected by centrifugation at 1,100 rpm for 6 min and re-suspended in platelet-poor plasma. Next, leukocyte-enriched plasma was centrifuged with a Percoll gradient (3 ml, 42–51%) at 1,100 rpm for 20 min. Neutrophils were found at the 42–51% Percoll layer interface. Red blood cells (RBC) were removed by RBC Lysis Buffer, and neutrophils were collected by centrifugation at 3,000 rpm for 5 min. Finally, neutrophils were re-suspended in RPMI 1640 with 10% Fetal bovine serum and 1% streptomycin and penicillin (Mediatech, USA).

For the measurement of pro-inflammatory cytokines, isolated human neutrophils were cultured with or without 0.55 β Escherichia coli LPS (100 ng/ml) in 24-well plates, and they were treated with BMS-470539 (1, 10, and 100 µM). The levels of tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-1β in neutrophils were measured using enzyme-linked immunosorbent assay (ELISA) kits (R & D Systems, USA), according to the manufacturer’s instructions.

Phosphorylation of mitogen-activated protein kinases (MAPKs) was determined as follows: neutrophils (5 x 10⁶/ml) were incubated for 30 min with or without LPS (100 ng/ml) in 24-well plates, and they were treated with BMS-470539 (100 µM). Intracellular levels of phosphorylated p38 MAPK, extracellular signal-regulated kinases 1/2 (ERK1/2) and c-Jun N-terminal kinase (JNK) were measured in cultured neutrophils using SimpleStep ELISA Kit (Abcam, UK), according to manufacturer's instructions. Separately, nuclear levels of nuclear factor kappa B (NF-kB) were measured with the same protocol described above.

Neutrophil apoptosis was evaluated with fluorescein isothiocyanate annexin V/propidium iodide (FITC-annexin V/PI) according to the manufacturer’s instructions (BD Biosciences, USA), with minor changes. Neutrophils were cultured with or without LPS (100 ng/ml), and treated with BMS-470539 (100 µM) for 24 h at 37°C. They were washed with PBS and centrifuged twice at 3,000 rpm for 5 min, after which the cells were incubated with 300 µl binding buffer containing annexin V/PI for 15–20 min, followed by flow cytometry within 1 h after annexin V/PI labeling. Neutrophils undergoing apoptosis were determined by positive FITC-annexin V staining and negative PI staining.

Data are expressed as the mean ± SD for each group and analyzed by one-way analysis of variance followed by Tukey-Kramer multiple comparisons test or Student's t-test using SPSS version 21. Statistical significance was defined as P < 0.050.

Results

Effects of BMS-470539 on the secretion of pro-inflammatory cytokines by LPS-stimulated neutrophils

There was a marked increase in the production of TNF-α, IL-6, and IL-1β when stimulated with LPS (Fig. 1). Compared to LPS-stimulation alone, treatment with BMS-470539 in LPS-stimulated neutrophils was associated with a significant reduction of
TNF-α production at concentrations of 1 µM (ΔTNF-α = −388.9 [95% CI: −494.3, −283.5], P < 0.001), 10 µM (ΔTNF-α = −338.2 [−443.7, −232.8], P < 0.001), and 100 µM (ΔTNF-α = −436.2 [−541.6, −330.7], P < 0.001). In the same condition above, treatment with BMS-470539 was associated with a significant reduction of IL-6 production at concentrations of 1 µM (ΔIL-6 = −383.8 [-572.8, -194.7], P < 0.001), 10 µM (ΔIL-6 = −287.4 [-476.4, -98.3], P = 0.003), and 100 µM (ΔIL-6 = −254.8 [-443.8, -65.8], P = 0.008). Likewise, treatment with BMS-470539 was associated with a significant reduction of IL-1β production at concentrations of 10 µM (ΔIL-1β = -94.6 [-158.0, -31.1], P = 0.002) and 100 µM (ΔIL-1β = -90.6 [-154.1, -27.1], P = 0.004), but not at concentrations of 1 µM (ΔIL-1β = -45.9 [-109.3, 17.6], P = 0.213). BMS-470539 alone did not increase the production of TNF-α, IL-6, and IL-1β in human neutrophils over the range of concentrations examined.

**Effects of BMS-470539 on the MAPKs and NF-κB activation in LPS-stimulated neutrophils**

There was a significant increase in the expression of phosphorylated p38, ERK1/2, and JNK in LPS-stimulated neutrophils when compared to control neutrophils (Δp38 = 0.208 [0.111, 0.304], P < 0.001; ΔERK1/2 = 0.215 [0.146, 0.284], P < 0.001; ΔJNK = 0.630 [0.510, 0.750], P < 0.001) (Fig. 2). Compared to LPS-stimulation alone, treatment with BMS-470539 (100 µM) was associated with a significant reduction of phosphorylated p38, ERK1/2, and JNK (Δp38 = -0.110 [-0.207, -0.013], P = 0.025; ΔERK1/2 = -0.075 [-0.144, -0.006], P = 0.031; ΔJNK = -0.285 [-0.405, -0.165], P < 0.001).

Similarly, there was a significant increase in the nuclear translocation of NF-κB in LPS-stimulated neutrophils when compared to control neutrophils (ΔNF-κB = 0.563 [0.390, 0.735], P < 0.001) (Fig. 3). Compared to LPS-stimulation alone, treatment with BMS-470539 (100 µM) was associated with a significant reduction of the nuclear translocation of NF-κB (ΔNF-κB = -0.278 [-0.450, -0.105], P = 0.002).

**Effect of BMS-470539 on LPS-delayed neutrophil apoptosis**

Fig. 4A shows typical diagrams of FITC-annexin V/PI flow cyto-

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**Fig. 1.** The effects of BMS-470539 on pro-inflammatory cytokine (TNF-α, IL-6, and IL-1β) production in human neutrophil stimulated by lipopolysaccharide (LPS). Neutrophils (5 × 10⁶/ml) from human blood were incubated for 4 h without or with BMS-470539 (1 µM, 10 µM, and 100 µM), or with LPS (100 ng/ml) or LPS plus BMS-470539 (Control, BMS, LPS, LPS + BMS, respectively). The level of cytokine (A) TNF-α, (B) IL-6, and (C) IL-1β were obtained from ELISA. Values are presented as mean ± SD (n = 6 per group). *P < 0.05 versus control, †P < 0.05 versus LPS.
tometry obtained after LPS, BMS-470539, or LPS plus BMS-470539 exposure, and the percentage of neutrophil apoptosis was measured by positive FITC-annexin V staining and negative PI staining (Fig. 4B). LPS stimulation inhibited neutrophil apoptosis compared to the controls (Δapoptosis = -19.38 [-23.13, -15.64], P < 0.001) (Fig. 4B). Compared to LPS-stimulation alone, BMS-470539 treatment significantly reversed LPS-induced inhibition of neutrophil apoptosis (Δapoptosis = 8.56 [4.81, 12.30], P < 0.001). BMS-470539 alone did not affect neutrophil apoptosis.

Discussion

In the present study, BMS-470539 reduced LPS-induced production of pro-inflammatory cytokines in human neutrophils, and attenuated phosphorylation of signaling molecules including MAPKs and NF-κB. BMS-470539 also inhibited LPS-delayed neutrophil apoptosis. These results demonstrate that BMS-470539, the first small-molecule MC1R selective agonist, may provide anti-inflammatory and immunomodulatory effects on human neutrophils in an excessive inflammatory condition.

Melanocortin peptides have been shown to be immunoprotective in various acute and chronic models of inflammation [10].
Especially, the anti-inflammatory actions of α-melanocyte-stimulating hormone (α-MSH), an endogenous melanocortin peptide, have been widely studied. α-MSH shows high affinity for MC1R, and many of the anti-inflammatory activities of α-MSH are thought to be related with MC1R among five distinct subtypes of melanocortin receptors (MC1R, MC2R, MC3R, MC4R, and MC5R). However, the anti-inflammatory roles of MC1R have been less evident because of the lack of selective ligands for in vivo studies until the discovery of BMS-470539 [7].

Patruno et al. [11] demonstrated that BMS-470539 reduced LPS-induced release of IL-6, IL-10, IL-8, and CCL-2 in macrophages in a dose-dependent manner up to 50 μM. In the present study, BMS-470539 also reduced the release of TNF-α and IL-6 (at 1 μM, 10 μM, and 100 μM), and IL-1β (at 10 μM and 100 μM) in human neutrophils. These results are consistent with previous studies showing that nonselective melanocortin peptides have
demonstrated a reduction in TNF-α, IL-6, and IL-1α [12,13]. However, the inhibitory effects of BMS-470539 on the production of TNF-α and IL-6 appeared not to be dose-dependent within the 1–100 μM range tested in the present study (‘possible ceiling effect’), while the production of IL-1β was not significantly reduced at 1 μM of BMS-470539. This result suggests that the optimal dosage of BMS-470539 to inhibit the production of anti-inflammatory cytokines is seemingly different for each cytokine. Furthermore, Kang et al. [8] reported that BMS-470539 (15 μmol/kg) was effective in reducing LPS-induced TNF-α levels but not the levels of IL-1β, IL-6, and IL-10 in mice. Therefore, further in vitro and in vivo studies with various doses will be required to determine the effects of BMS-470539 on the production of pro-inflammatory cytokines.

LPS treatment promotes NF-κB activation and the synthesis of pro-inflammatory cytokines [14]. Several studies have suggested that α-MSH reduces the expression of pro-inflammatory cytokines by inhibiting NF-κB activation [15,16]. Consistent with this melanocortin-induced effect, BMS-470539 inhibited activation of a NF-B-luciferase reporter and nuclear translocation of NF-κB in TNF-α-induced human melanoma cell line [8]. However, the ability of BMS-470539 to inhibit activation of NF-κB in immune cells was not investigated before. In the present study, we have demonstrated that BMS-470539 inhibits nuclear translocation of NF-κB in human neutrophils treated with LPS. This ability of BMS-470539 seems to result in the blunting of the inflammatory response by decreased cytokine accumulation.

BMS-470539 also attenuated the LPS-induced phosphorylation of MAPKs including p38, ERK1/2, and JNK in human neutrophils in the present study. Neutrophil intracellular signal transduction appears to utilize the above three major MAPK cascades [17], which play critical roles in the generation of pro-inflammatory cytokines [18]. LPS is known to activate these MAPKs [19]. Cloudier et al. [20] demonstrated that the inhibition of MAPK pathways substantially attenuated the release of pro-inflammatory cytokines without cross-talk between the MAPK and NF-κB pathways. Therefore, MC1R activation may reduce LPS-induced pro-inflammatory cytokines by inhibition of MAPK pathways as well as NF-κB pathway in human neutrophils.

Neutrophil apoptosis is known to be inhibited by inflammatory cytokines or bacterial products such as LPS. Consistent with other studies, LPS reduced neutrophil apoptosis in the present study, and this reduction was attenuated by MC1R agonist BMS-470539. Reduced pro-inflammatory cytokines by BMS-470539 might be a reason of modulating neutrophil apoptosis. In addition, inhibitory effect of BMS-470539 on MAPKs activation might also be another possible mechanism. Nolan et al. [21] demonstrated the opposing roles of MAPKs in mediating neutrophil apoptosis after LPS stimulation. They showed that both ERK and p38 were activated by LPS; however, ERK signaling inhibited apoptosis while p38 signaling promoted apoptosis. In the present study, all ERK, p38, and JNK phosphorylations were activated by LPS, and attenuated by BMS-470539. Therefore, the precise mechanism of modulating neutrophil apoptosis by BMS-470539 could not be confirmed in the present study.

In conclusion, BMS-470539 can suppress the inflammatory responses of LPS-stimulated neutrophils by inhibition of MAPK pathways or NF-κB pathway, and it can also inhibit LPS-delayed neutrophil apoptosis. These results suggest the possibility of MC1R selective agonists as novel therapeutic agents in the future for modulating prolonged and excessive inflammatory conditions, such as severe sepsis.

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**Conflicts of Interest**

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

**Author Contributions**

Seongheon Lee (Visualization; Writing – review & editing)

Wan Ju (Writing – original draft)

Tran Duc Tin (Investigation; Methodology)

Joungmin Kim (Resources; Validation)

Jeong Seok Lee (Writing – review & editing)

Cheon Hee Park (Supervision; Validation)

Sang-Hyun Kwak (Funding acquisition; Investigation; Methodology; Project administration; Supervision)

**ORCID**

Seongheon Lee, https://orcid.org/0000-0002-2675-2521

Wan Ju, https://orcid.org/0000-0002-6700-2436

Tran Duc Tin, https://orcid.org/0000-0003-0097-4465

Joungmin Kim, https://orcid.org/0000-0003-1135-1968

Jeong Seok Lee, https://orcid.org/0000-0003-2085-1091

Cheon Hee Park, https://orcid.org/0000-0001-7986-8416

Sang Hyun Kwak, https://orcid.org/0000-0001-6077-2086
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Continuous quadratus lumborum block as part of multimodal analgesia after total hip arthroplasty: a case report

Hahyeon Bak, Seunguk Bang, Subin Yoo, Seoyeong Kim, So Yeon Lee

Departments of Anesthesiology and Pain Medicine, Daejeon St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Daejeon, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Commonly used epidural or systemic analgesics for pain control after hip surgery carry risk for potential adverse effects. In contrast, the quadratus lumborum block (QLB) utilizes a simple and easy fascial plane technique and provides a wide area of sensory blockade. Thus, the QLB may be beneficial as analgesia after total hip arthroplasty.

Case: Here, we report the case of an 83-year-old man who received a continuous transmuscular QLB as part of a multimodal analgesia after hardware removal and total hip arthroplasty. The patient received a continuous infusion of 0.2% ropivacaine at 8 ml/h through an indwelling catheter in addition to patient-controlled analgesia with intravenous fentanyl and oral celecoxib. The patient’s pain scores did not exceed 4, and no additional analgesics were required until postoperative day 5.

Conclusions: Transmuscular QLB may be a suitable option for multimodal analgesia after total hip arthroplasty.

Keywords: Analgesia; Arthroplasty; Catheters; Nerve block; Pain; Ropivacaine; Ultrasonography.
Case Report

An 83-year-old man weighing 64 kg presented with loosened hip screws one year after proximal femoral nail antirotation. Hardware removal and right-sided total hip arthroplasty were planned, and the patient provided written informed consent for the use of a QLB and publication of this report, which was approved by the Institutional Review Board of The Catholic University of Korea, Daejeon St. Mary’s Hospital (DC17ZESI0092). The patient had a history of hypertension and benign prostatic hypertrophy, both of which were well controlled by medication. He had previously undergone kyphoplasty for a compression fracture in the L1 vertebra. Otherwise, his history assessment and preoperative evaluation were unremarkable.

In the operating room, after standard monitoring was implemented, fentanyl 50 µg and midazolam 1 mg were intravenously administered for sedation and analgesia. The patient was then placed in a left lateral decubitus position, and epidural anesthesia was induced at the level of the L4–L5 interspace using the median approach with an 18-gauge Tuohy epidural needle. Loss of resistance to 1 ml of normal saline was achieved on the first attempt, and a test dose comprised of 1% mepivacaine 3 ml and epinephrine 15 g was administered, followed by a bolus comprised of 0.5% ropivacaine 13 ml and fentanyl 50 µg.

Following the epidural procedure, a transmuscular QLB was performed under ultrasound guidance following an acute pain service protocol. Subsequent to the placement of a 2- to 7-MHz curved ultrasound probe over the midaxillary line, the external oblique, internal oblique, and transversus abdominis muscles were identified along with the transversus abdominis aponeurosis. The probe was moved to trace the muscles (quadratus lumborum [QL], psoas major, and erector spinae) in the anterior to posterior direction using the shamrock sign. After skin infiltration with 1% mepivacaine 2 ml, an 18-gauge, 90 mm Tuohy needle attached to intravenous extension tubing between the needle and syringe was inserted in the posterior to anterior direction. The needle was aimed between the QL and psoas major muscles (Fig. 1). After confirmation of the needle position via injection of 2 ml of saline,

Fig. 1. Schematic diagram. The target of the injection point is the fascial plane between the quadratus lumborum muscle and the psoas muscle. EOM: external oblique muscle, IL: ilio-costalis lumborum muscle, IOM: internal oblique muscle, LD: latissimus dorsi muscle, Lo: longissimus muscle, Mu: multifidus muscle, PM: psoas muscle, QL: quadratus lumborum muscle, TAM: transversus abdominis muscle, TP: transverse process.
a 19-gauge epidural catheter was inserted 2 cm through the epidural needle under real-time ultrasound guidance (Fig. 2). Accurate catheter placement was confirmed by Doppler ultrasonography. Following catheter placement, the patient was returned to the supine position, and his condition was confirmed to be stable before proceeding with surgery.

The patient was intraoperatively sedated by continuous propofol infusion. His vital signs remained stable during surgery, which was completed uneventfully. No additional analgesics were required. The total operation time was 3 h and 30 min. At the end of surgery, the patient received intravenous ketorolac 30 mg and ramosetron 0.3 mg: 25 ml of a prepared mixture of 0.2% ropivacaine and 5 µg/ml of epinephrine was injected through the indwelling catheter.

The multimodal postoperative analgesia regimen included oral medication, intravenous analgesia, and regional anesthesia, with rescue analgesics available on demand. This regimen was in accordance with the acute pain service protocol at our hospital. The patient was prescribed oral celecoxib 200 mg twice daily for seven days. The 0.2% ropivacaine and epinephrine mixture was continuously infused at a rate of 8 ml/h through the indwelling catheter, using a patient-controlled analgesia (PCA) pump (Hospira Gem-Star® Pump, Hospira Inc., USA). Intravenous fentanyl was also provided using a second PCA pump (Hospira) with the following settings: demand dose, 30 µg (0.5 µg/kg); no basal infusion; lock-out time, 7 min; and a 4 h limit of 240 µg (4 µg/kg). Postoperative pain was assessed using a visual analogue scale (VAS). If the VAS score exceeded 4, the patient was eligible to receive intravenous tramadol 25 mg and meperidine 25 mg as rescue analgesics as per our protocol.

In the post-anesthesia care unit, the patient experienced no pain because of residual epidural anesthesia. However, he complained of shivering, so a forced-air warming blanket was provided and intravenous meperidine 25 mg was administered. Four hours after surgery, the patient reported that his dorsiflexion, plantar flexion, and the knee flexion returned to his usual range of motion bilaterally. Assuming that the epidural anesthetic effect had worn off, we evaluated the patient's sensory blockade, motor blockade, and pain scores. His resting and dynamic VAS scores were 2 and 4, respectively. He showed sensory blockade from T8 to L3 at the midaxillary line (T8–9: decreased pinprick sensation relative to the contralateral side; T10–L3: no pinprick sensation of pain). Moreover, he showed mild weakness against resistance during right knee extension but no issue with flexing and extending his left knee against both gravity and resistance.

The patient's resting and dynamic VAS scores remained stable at 2–3 and 3–4, respectively, at 4, 12, and 24 h after surgery. In fact, all resting and dynamic pain scores were 1–2 and 1–3, respectively, throughout postoperative day 5 (Fig. 3). Monitoring the VAS score of the patient settled below 4, perineural PCA was discontinued at 48 h after surgery, and intravenous PCA was dis-

![Fig. 2. Ultrasound guided transmuscular quadratus lumborum block. After placing a curved probe perpendicular to the vertebral axis, the transverse process and three associated muscles (quadratus lumborum, psoas major, and erector spinae muscle) were found using the shamrock approach. After proper needle position was confirmed with saline, a 19-gauge epidural catheter was inserted over 2 cm. Proper placement was confirmed by saline injection under real-time ultrasound. ESM: erector spinae muscle, LD: Latissimus dorsi muscle, PM: psoas muscle, QLM: quadratus lumbarum muscle, S: saline, TLF: thoracolumbar fascia, TP: transverse process, VB: vertebral body, arrow heads: needle.](https://doi.org/10.4097/kja.d.19.00016)

![Fig. 3. Pain score at rest and with movement. The pain score was assessed for five days, postoperatively. Dotted line: resting pain, solid line: dynamic pain. VAS: visual analogue scale, PCA: patient-controlled analgesia, D: days.](https://doi.org/10.4097/kja.d.19.00016)
continued on postoperative day 5, in accordance with our hospital protocol. The patient’s fentanyl consumption was tracked using the PCA program. He received the first demand dose of fentanyl 30 µg through the PCA pump at 17 h after surgery. During the first 48 h, he pressed the PCA button four times, and his total fentanyl consumption was 120 µg. He pressed the PCA button twice on day 3, three times on day 4, and nine times on day 5. None of the pain scores exceeded 4, and no rescue analgesics were required during the first five postoperative days. At the 1 week and 1 month follow-up visits, the patient did not exhibit residual sensory-motor deficits or complain of symptoms suggestive of a neurological injury.

**Discussion**

The main origins of acute pain after total hip arthroplasty include the hip joint and incision site. Prior study has provided support for the LPB as an effective regional analgesic after total hip arthroplasty, with less opioid consumption compared to conventional systemic analgesia [6]. In a double-blind prospective trial, for example, the LPB provided enhanced analgesia and significantly reduced cumulative morphine consumption in the plexus group (5.6 ± 4.7 mg) as compared to the control group (12.6 ± 7.5 mg) until 6 h after randomization [6]. However, even with ultrasound guidance, the LPB is technically difficult to perform and carries a risk of serious complications [3]. Transmuscular QLB may be an effective alternative analgesic to the LPB. The QLB has been successfully used for surgical anesthesia during lower extremity amputation [7], as well as minimally invasive and total hip arthroplasty [8]. In our present case, the patient received a continuous transmuscular QLB as part of a multimodal analgesia after hardware removal and total hip arthroplasty. Notably, the patient did not request analgesic agents, beyond the perineural infusion and regularly scheduled oral celecoxib, until 17 h following surgery. Furthermore, our patient’s total opioid consumption during the first 48 h post-surgery was equivalent to 12 mg of morphine (fentanyl 120 µg) while about 40 mg of morphine was administered until the first 48 h in the study of Stevens et al. [6], indicating that this multimodal analgesia regimen was highly effective. In one cadaveric study, the transmuscular QLB demonstrated consistent spread of the local anesthetic to the L1 to L3 nerve roots, covering the genitofemoral, femoral, and obturator nerves [5]. In another cadaveric study, the transmuscular QLB resulted in the spread of the local anesthetic to the lumbar paravertebral space in 63% of the specimens, with the solution reaching the upper branches of the lumbar plexus and psoas major muscle in 70% of the specimens [9]. Consistent with the observed spread of anesthetic in cadavers following the QLB, patients receiving a QLB have reported lower extremity muscle weakness [10], and a retrospective study demonstrated that 357 of 2,382 patients showed evidence of quadriceps muscle weakness after all type of QLB (transmuscular QLB). Notably, the incidence was as high as 90% in anterior QLB [11].

We hypothesize that the transmuscular QLB provides effective analgesia after hip surgery, because this method partially or totally blocks the lumbar plexus (T12–L4), which innervates the hip joint and the incision site. After the QLB, our patient showed sensory blockade from T8 to L3. This sensory blockade presumably provided analgesia for the hip joint as well as the incision site through blockade of the lateral femoral cutaneous nerve (L2–3), subcostal nerve (T12), and ilioinguinal and iliohypogastric nerves (L1) [12].

Although our patient could extend the knee against both gravity and resistance, he exhibited decreased strength against resistance. There are two possible explanations for this finding. First, the local anesthetic solution spread to the L3 spinal nerve, because of which the femoral nerve (L2–4) was partially blocked. Second, although unlikely, differential blockade could have occurred because of the infusion of 0.2% ropivacaine instead of a more diluted solution through the catheter.

Additionally, it is known that the severity of pain decreases and the risk of catheter-related infection increases rapidly 48 h after total hip arthroplasty [13–15], so the catheter was removed 48 h after surgery. Although the indwelling catheter was removed at 48 h after surgery, the patient’s pain remained well controlled through postoperative day 4, following which his analgesic requirement sharply increased. In a follow-up interview, the patient reported that he only pressed the PCA button when his pain score was ≥ 4, in accordance with our acute pain service protocol. It remains unclear whether the prolonged analgesia after removal of the perineural catheter in our patient was a result of the QLB, although a previous case report has described prolonged analgesia after a QLB [4]. Further prospective studies are required to clarify this finding.

In summary, we described the successful use of a continuous transmuscular QLB as part of a multimodal analgesia regimen after total hip arthroplasty. Notably, the QLB provided highly effective analgesia without significant motor blockade. In addition, the block was technically easy to perform because the key targets could be easily located under ultrasound guidance; this also decreases the risk of complications. The findings from this case suggest that the continuous transmuscular QLB is a suitable alternative to the LPB for multimodal analgesia after total hip arthroplasty; however, additional case reports and prospective, randomized control trials are needed to further clarify our findings.

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Conflicts of Interest

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

Author Contributions

Hahyeon Bak (Data curation; Writing – original draft)
Seunguk Bang (Conceptualization; Writing – original draft; Writing – review & editing)
Subin Yoo (Data curation; Writing – original draft)
Seoyeong Kim (Data curation; Writing – original draft)
So Yeon Lee (Data curation; Writing – original draft)

ORCID

Hahyeon Bak, https://orcid.org/0000-0002-5261-2135
Seunguk Bang, https://orcid.org/0000-0001-6609-7691
Subin Yoo, https://orcid.org/0000-0001-6487-2914
Seoyeong Kim, https://orcid.org/0000-0002-2313-3258
So Yeon Lee, https://orcid.org/0000-0002-2749-1941

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Ultrasound-guided percutaneous intercostal cryoanalgesia for multiple weeks of analgesia following mastectomy: a case series

Rodney A. Gabriel1,2*, John J. Finneran1*, Matthew W. Swisher1, Engy T. Said1, Jacklynn F. Sztain1, Bahareh Khatibi1, Anne M. Wallace2, Ava Hosseini3, Andrea M. Trescot4, Brian M. Ilfeld1*

Departments of 1Anesthesiology, Division of Regional Anesthesia and Acute Pain, 2Medicine, Division of Biomedical Informatics, 3Surgery, University of California, San Diego, La Jolla, CA, 4Pain and Headache Center, Eagle River, AK, USA

Background: Acute post-mastectomy pain is frequently challenging to adequately treat with local anesthetic-based regional anesthesia techniques due to its relatively long duration measured in multiple weeks.

Case: We report three cases in which preoperative ultrasound-guided percutaneous intercostal nerve cryoneurolysis was performed to treat pain following mastectomy. Across all postoperative days and all three patients, the mean pain score on the numeric rating scale was 0 for each day. Similarly, no patient required any supplemental opioid analgesics during the entire postoperative period; and, no patient reported insomnia or awakenings due to pain at any time point. This was a significant improvement over historic cohorts.

Conclusions: Ultrasound-guided percutaneous cryoanalgesia is a potential novel analgesic modality for acute pain management which has a duration that better-matches mastectomy than other currently-described techniques. Appropriately powered randomized, controlled clinical trials are required to demonstrate and quantify both potential benefits and risks.

Keywords: Acute pain; Cryoanalgesia; Cryoneurolysis; Mastectomy; Regional anesthesia.

Poorly controlled post-mastectomy pain remains a challenge often leading to persistent postsurgical pain lasting months to years [1]. Due to its typical duration of multiple weeks, post-mastectomy pain is frequently challenging to adequately treat with local anesthetic-based regional anesthesia techniques which provide multiple hours or days of analgesia (e.g., single injection nerve blocks or continuous nerve blocks, respectively). Ultrasound-guided percutaneous cryoneurolysis is an alternative regional analgesic modality that reversibly induces peripheral nerve Wallerian degeneration using extremely cold temperatures, yet spares the endo-, peri-, and epineurium along which the nerve regenerates at approximately 1–2 mm/d. The result is a temporary sensory and motor nerve block with a duration measured in weeks and occasionally months without any delivery device to manage or infusion pump to remove [2]. While described extensively in the chronic pain literature [3], recently published case reports support the use of ultrasound-guided percutaneous cryoneurolysis for the treatment of acute postoperative pain [2,4–6]. Given its analgesic duration roughly corresponds to that of post-mastectomy

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Corresponding author:
Rodney A. Gabriel, M.D., MAS
Department of Anesthesiology, Division of Regional Anesthesia and Acute Pain, University of California, San Diego, La Jolla, CA 92037, USA
Tel: +1-858-663-7747
Email: ragabriel@ucsd.edu
ORCID: https://orcid.org/0000-0003-4443-0021

*Outcomes Research Consortium (Cleveland, Ohio, USA)
pain, cryoanalgesia is a possible analgesic option. We now report three cases in which preoperative ultrasound-guided percutaneous intercostal nerve cryoneurolysis was performed to treat pain following mastectomy.

Case Reports

All patients (n = 3) provided written, informed consent for unidentifiable inclusion in subsequent publications. The University of California San Diego Institutional Review Board (San Diego, CA) waives review requirements for case reports. A curvilinear ultrasound probe (C60, Sonosite, USA) was used for all procedures. All patients had an ipsilateral ultrasound-guided paravertebral catheter inserted at either T3 or T4 lateral approximately 2.5 cm from the midline using a technique previously described [7], followed by an injection into the perineural catheter of ropivacaine 0.5% with epinephrine (1 : 400,000) in divided doses with gentle aspiration every 2–3 ml. Bilateral catheters were inserted for bilateral mastectomy procedures.

Immediately after placement of the paravertebral catheter(s), ultrasound-guided percutaneous cryoanalgesia was performed on four proximal ipsilateral intercostal nerves: T2–5, approximately 5 cm from the midline. The sterile field and ultrasound transducer cover used for the perineural catheter insertion were used for the subsequent cryoneurolysis procedure. The intercostal artery was identified caudad to the respective rib in the parasagittal plane with a short-axis view. Lidocaine 1% was injected subcutaneously to ensure topical anesthesia. A 14-gauge angiocatheter was advanced towards the target nerve leaving the tip within the internal intercostal muscle prior to reaching the nerve itself. The angiocatheter needle was withdrawn leaving the angiocatheter in place.

The 90 mm cryoprobe (Iovera Smart Tip, Myoscience, USA) was introduced via the angiocatheter and advanced to the T2 intercostal nerve under in-plane ultrasound guidance (Fig. 1). Three cycles of 2 min of freezing followed by a 1-min thawing period were applied and the probe subsequently withdrawn. This procedure was repeated on the next three intercostal nerves. For bilateral mastectomies, the cryoneurolysis procedure was repeated on the contralateral side.

All patients received a general anesthetic without complications. Within the recovery room the perineural catheter(s) were attached to portable pump(s) which infused ropivacaine 0.2% 8 ml/h basal with an optional patient-controlled 4 ml bolus available every 30 min (every 60 min for bilateral catheters). Catheters were removed the morning of postoperative day 2 prior to home discharge, and patients given a prescription for oxycodone (5 mg tablets) to be taken if needed. All patients were called by telephone on postoperative days 1–4, 7, 14, 21, and 28. Patient #1 was a 46-year-old woman with hormone receptor positive, Her2-negative breast cancer who underwent left-sided mastectomy and received a T4 paravertebral catheter. Patient #2 was a 45-year-old woman with hormone receptor positive, Her2-negative invasive ductal carcinoma who underwent left-sided mastectomy with axillary sentinel node biopsy who received a T3 paravertebral catheter. Patient #3 was a 47-year-old woman with hormone receptor negative breast cancer who underwent bilateral mastectomy with left-sided axillary node biopsy and received bilateral T3 paravertebral catheters.

Across all postoperative days and all three patients, the mean pain score on the numerical rating scale (NRS) was 0 for each day (Fig. 2 which includes published controls for comparison). Similarly, no patient required any supplemental opioid analgesics in the entire postoperative period (Fig. 3 which includes published controls for comparison). Similarly, no patient reported insomnia or awakenings due to pain at any time point. No complications related to cryoanalgesia were reported in any patient.

Discussion

We describe three cases in which preoperative ultrasound-guided percutaneous intercostal cryoanalgesia provided a nearly pain-free postoperative course following uni- and bilateral mastectomies without requiring supplemental oral analgesics. This is noteworthy considering this surgical procedure usually results in pain that outlasts a single-injection nerve block and breaks through even a continuous perineural local anesthetic infusion, resulting in supplemental opioid requirements [7].

We provided a continuous paravertebral nerve block to the three patients described in this report since there were no similar previously-published cases (that we are aware of) to suggest the degree of cryo-induced analgesia that might be expected, and we wanted to provide our current standard-of-care analgesics. In addition, our primary aim was to provide potent analgesia following perineural catheter withdrawal prior to discharge on postoperative day 2, and not replace the single-injection and/or continuous nerve blocks. However, as it happens, the cryoneurolysis appears to have provided significant benefit even during the ropivacaine infusion since these three patients reported almost no pain at all, while published controls from our own institution and receiving a similar continuous paravertebral ropivacaine infusion reported a median (interquartile) NRS of 3.6 (2.0–4.0) the day following mastectomy [1]. Apparent related benefits of the cryoanalgesia may be found in the increased quality of sleep, with these three patients reporting no insomnia due to pain, compared with 30%,
Percutaneous ultrasound-guided cryoanalgesia has been previously described for a few acute pain indications, both perioperative and unrelated to surgery [2, 4–6]. However, its application to mastectomy appears to be particularly suitable due to various factors, including (1) the near-total coverage of the surgical site with the blocks; (2) the relative insignificance of cryo-induced sensory and motor block; and, (3) the similar durations of post-mastectomy pain and cryoneurolysis. Importantly, the development of persistent postsurgical pain is associated with the level of pain experienced in the immediate postoperative period; and multiple studies have demonstrated decreased chronic pain with improved analgesia in the 2–3 d following mastectomy [8, 9]. Considering the du-

Fig. 1. Ultrasound image of cryoprobe advancing towards intercostal nerve. (A) proximal short-axis view (5 cm lateral to spinous process) of ribs where intercostal nerve blocks are performed, (B) rendering of Fig. 1A labeling ribs, pleura, and intercostal artery (red circle), (C) view with cryoprobe in-plane next to target, (D) rendering of Fig. 1C with trocar labeled, (E) view with ice-ball formation at tip of cryoprobe, (F) rendering of Fig. 1E with ice-ball labeled (blue circle).
ration of cryoanalgesia will usually match or extend beyond post-mastectomy pain—offering the possibility of a relatively pain-free surgical experience—this modality has the potential to significantly decrease the risk of persistent postsurgical pain.

Direct comparisons with continuous peripheral nerve blocks are unavailable, but some theoretical benefits of cryoneurolysis include an ultra-long duration of action, no catheter insertion/removal, no required infusion management/oversight, the lack of an infusion pump and anesthetic reservoir to carry, a considerably lower risk of infection, and no risk of local anesthetic toxicity, catheter dislodgement, or fluid leakage [10]. Risks include bleeding, bruising, and—if the ice ball involves the skin—frostbite, alopecia, depigmentation, and/or hyperpigmentation. Other disadvantages include the requirement of an initial capital investment for the cryoneurolysis machine (although subsequent per-patient costs are relatively low) [11]; a somewhat unpredictable duration of action [12]; and frequent dense sensory and motor blocks (less consequential following mastectomy, but significant for other surgical procedures and treated nerves) [3].

With over 50 years of clinical use, the published literature suggests cryoneurolysis has a level of safety surpassing traditional local anesthetic-based peripheral nerve blocks. However, it is noteworthy that two randomized, controlled investigations reported a statistically significant increase in the incidence of neuropathic pain for cryoneurolysis administered via the surgical incision in subjects at 8 weeks (resolving by 6 months) [13], 6 months, and 1 year following open thoracotomy [14]. In contrast, the majority of randomized, controlled trials of cryoneurolysis via the surgical incision did not report any increased risk of persistent postoperative pain, although a few additional small studies did note a possible association that did not reach statistical significance [15]. The reasons for these discrepancies remain unknown, and due to a myriad of confounding variables among studies, no causal inferences can be made without additional data. Considering the lack of reports of chronic pain following cryoneurolysis for other indications [3], this may be an issue related exclusively to thoracotomy—possibly related to the double-crush theory.

In summary, ultrasound-guided percutaneous cryoanalgesia is a potential novel modality for acute pain management following mastectomy. Benefits may potentially extend beyond the duration of the cryoneurolysis with a decrease in the incidence and severity of chronic postoperative pain. Appropriately powered randomized, controlled clinical trials are required to demonstrate and quantify both potential benefits and risks.
Funding Statement

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Conflicts of Interest

Drs. Wallace and Hosseini: No potential conflict of interest relevant to this article was reported.

Author Contributions

Rodney Allanigue Gabriel (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing)
John J. Finneran (Conceptualization; Writing – original draft; Writing – review & editing)
Matthew W. Swisher (Conceptualization; Writing – original draft; Writing – review & editing)
Engy T. Said (Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing)
Jacklynn F. Sztain (Writing – original draft; Writing – review & editing)
Bahareh Khatibi (Writing – original draft; Writing – review & editing)
Anne M. Wallace (Conceptualization; Methodology; Writing – original draft; Writing – review & editing)
Ava Hosseini (Methodology; Writing – original draft; Writing – review & editing)
Andrea M. Trescot (Conceptualization; Methodology; Writing – original draft; Writing – review & editing)
Brian M. Ilfeld (Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing)

ORCID

Rodney A. Gabriel, https://orcid.org/0000-0003-4443-0021
John J. Finneran, https://orcid.org/0000-0002-0955-155X
Matthew W. Swisher, https://orcid.org/0000-0003-2196-6288
Engy T. Said, https://orcid.org/0000-0002-7897-1670
Jacklynn F. Sztain, https://orcid.org/0000-0001-6215-5428
Bahareh Khatibi, https://orcid.org/0000-0003-1954-1731
Anne M. Wallace, https://orcid.org/0000-0003-2919-2491
Ava Hosseini, https://orcid.org/0000-0003-3731-2182
Andrea M. Trescot, https://orcid.org/0000-0001-8456-6340
Brian M. Ilfeld, https://orcid.org/0000-0002-6144-3273

References


Methodological issues on prediction of postoperative desaturation after spinal anesthesia in aging patients

Khosro Farhadi, Mehdi Naderi

Clinical Research Development Center, Taleghani and Imam Ali Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran

We carefully and enthusiastically reviewed the article by Jo et al. published in the August 2019 issue of the Korean Journal of Anesthesiology [1]. The purpose of their study was to survey postoperative desaturation prediction after spinal anesthesia in aging patients based on preoperative pulmonary function and arterial blood gas analysis. Therefore, the authors examined the medical records of three hundred thirty-nine of patients (age ≥ 80 years) who had a recorded history of undergoing femoral neck fracture surgery under spinal anesthesia [1]. Binary logistic regression analysis and receiver operating characteristic curves were used to investigate the predictors and predictive ability of early postoperative desaturation [1]. The authors reported that the PaO$_2$/FiO$_2$ ratio (OR = 0.972) and history of cardiovascular disease (OR = 2.127) predicted postoperative desaturation after femoral neck surgery using spinal anesthesia [1].

To develop and evaluate the prediction of a disease outcome or score and index, there are requirements to which studies must adhere. The first requirement is that the study design includes a cohort, which can be transformed into two separate cohorts or two cohorts of patients with failed or successful outcomes [2,3]. The second requirement is model validation, including internal and external validation, which uses the same data for internal validation but separate data for external validation. Various methods such as split file and bootstrapping, among others, can be used for validation. [2–5]. Thirdly, discrimination is defined as the ability to distinguish events from non-events, which is appropriately determined by area under the curve (AUC). One should always consider that a large AUC only reflects a high degree of discrimination, and it may become difficult to assess whether it is appropriate or not. Consequently, even if the AUC is statistically significant, there is a chance it won’t be predictive [3]. If the qualitative interaction between the important variables is not examined, it will lead to miscalculations of results [3].

The authors concluded that preoperative PaO$_2$/FiO$_2$ ratio might predict the postoperative desaturation in aging patients after spinal anesthesia for femoral fracture surgery, while preoperative arterial blood gas analysis may be helpful in predicting early postoperative desaturation in such patients [1]. In summary, for predictive studies, the above points should be duly considered, otherwise, prediction cannot be guaranteed despite a significant association [2,3]. In this letter, we explain the drawbacks of the article presented by Jo et al. and recommend that any predictive study should adhere to the above methodological requirements [2–5].

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

Khosro Farhadi (Conceptualization; Writing – original draft; Writing – review & editing)
Mehdi Naderi (Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing)

ORCID

Khosro Farhadi, https://orcid.org/0000-0001-9054-6557
Mehdi Naderi, https://orcid.org/0000-0002-5608-6582

References

We have read the study on the long-term prognosis of patients after discharge from the intensive care unit (ICU) [1]. The article reaffirms the existence of factors that cannot be modified during the ICU stay; however, other aspects may improve survival after discharge, such as preventative measures.

The authors have discussed some of the limitations; however, there are additional aspects that we feel are worthy of discussing for better acceptance of the results. Firstly, although the 1-year mortality data reported in the study is congruous with international data, we believe that the reported mortality is probably lower. The exclusion of 827 patients who died in the hospital or had a terminal prognosis from the final analysis is a potential bias. Furthermore, 673 patients were also excluded because of ICU readmission, the number of patients readmitted within 1 year and the mortality data are unclear. Therefore, the data represent the long-term outcome of ICU survivals and not patients who required ICU care.

Secondly, in comparison with the 1-year mortality data from 2006 to 2011, the 5-year mortality data presented only a sample size as the study was performed on only 831 patients from 2006 to 2007.

Thirdly, the authors did not report the impact of ICU length of stay, treatment modalities such as the length of mechanical ventilation weaning modalities, tracheostomy, presence of specialized weaning units [2], and renal replacement on survival. No data on the quality of life of survivors were mentioned, including transfer to long-term care facilities or receiving in-home mechanical ventilation during the follow-up period [3]. It is recommended to consider this data since it is a critical factor that can affect the long-term outcome after discharge. Similarly, as the authors evaluated the long-term outcome, information and analysis of the parameters related to the quality of life at discharge that can be modified would provide essential information. We believe that it could be more informative if the authors considered the evaluation of predictive models of survival [4].

Lastly, the study is a single-center, university-based study and does not reflect mortality among ICU in Korea. The data cannot be generalized to entire Korea due to different standard of care and implementation/adherence of protocols. This data can be helpful to minimize institutional variation in discharge protocols [5]. We applaud the authors for their work with a relatively correct sample size and multivariate analysis of factors and
would welcome the above information for better interpretation of their results.

**Conflicts of Interest**

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

**Author Contributions**

Antonio M Esquinas (Conceptualization; Data curation; Writing – original draft; Writing – review & editing)
Habib Md Reazaul Karim (Conceptualization; Resources; Writing – original draft; Writing – review & editing)
Bushra Mina (Formal analysis; Writing – review & editing)

**ORCID**

Antonio M Esquinas, https://orcid.org/0000-0003-0571-2050
Habib Md Reazaul Karim, https://orcid.org/0000-0002-6632-0491
Bushra Mina, https://orcid.org/0000-0001-8796-9591

**References**

I read with great interest the narrative review on awake supraglottic airway guided flexible bronchoscopic intubation in patients with anticipated difficult airways by Lim and Wong [1]. Undoubtedly, awake intubation is indicated in a patient when difficulty in maintaining or securing the airway after induction of general anesthesia is expected. The natural airway is better maintained in the awake patient. The normal muscle tone helps to maintain the anatomy and easier identification of upper airway structures relative to each other. There is less likelihood of aspiration with preservation of the lower esophageal sphincter tone and maintenance of spontaneous breathing; besides, the patient can follow instructions while awake. However, awake intubation requires careful patient preparation, adequate topical anesthesia of the airway, and judicious use of sedative agents; besides, an appropriate level of operator expertise. The insertion of a supraglottic airway device (SAD) seated in the pharynx above the laryngeal inlet attenuates the pressor and laryngeal responses [2]. It is reasonable to assume that in the awake patient, an SAD may be better tolerated than an endotracheal tube. The SAD serves as a conduit for fiberoptic bronchoscope-guided endotracheal intubation and, if positioned correctly, leads to easier and more rapid endotracheal intubation. The Difficult Airway Society guidelines for the management of the unanticipated difficult airway [3] and the American Society of Anesthesiologists Difficult Airway algorithm [4] suggest intubation through an SAD in case of failed tracheal intubation. Insertion of an SAD in the awake patient under topical anesthesia followed by tracheal intubation after induction of general anesthesia has been reported previously [3]. In their narrative review, Lim and Wong describe inserting an Ambu Auragain™ SAD after topical anesthesia of the airway and remifentanil infusion. Fiberoptic bronchoscope-guided tracheal intubation was achieved through the SAD. However, it is not clear why the authors did not inflate the SAD cuff. The position of an SAD is usually confirmed after cuff inflation. Cuff inflation permits the formation of a seal between the device and the pharyngeal mucosa; besides, the use of a second-generation SAD also allows isolation of the respiratory and alimentary tracts. Cuff inflation also prevents device displacement. There seems to be no recommendation in literature to leave the SAD cuff uninflated. Furthermore, insufflation of oxygen at 10–15 L/min through an oxygen tubing attached to the proximal end of the ventilation port of the SAD may lead to gastric insufflation, regurgitation, and pulmonary aspiration. The authors report supraglottic airway guided flexible bronchoscopic intubation in several cases. However, when coughing or patient movement during intubation is undesirable, as in patients with intracranial lesions or an unstable cervical spine, it may be prudent to administer general anesthesia with or without the use of muscle relaxants after confirmation of SAD position by fiberoptic bronchoscopy. This may be followed by assisted ventilation before attempting tracheal intubation through the SAD.
Conflicts of Interest

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

References


Response to comments on “Awake supraglottic airway guided flexible bronchoscopic intubation in patients with anticipated difficult airways: a case series and narrative review”

Patrick Wong, Wan Yen Lim

Department of Anesthesiology, Singapore General Hospital, Singapore, Singapore

We thank the authors for their reply; many of their initial statements were covered in our article. We agree that the cuff inflation (to 60 cmH\textsubscript{2}O) of a second-generation supraglottic airway device (SAD) allows for better airway seal. However, we keep the cuff deflated for various reasons: It minimizes the oropharyngeal pressure and may help relieve patient discomfort; it avoids the risk of obscuring the glottic view; and the cuff can be inflated later, if required, for instance, for positive pressure ventilation. In one study, with no cuff inflation, the optimal glottic view (only cords seen) occurred in 30% of patients compared to the 0% occurring with an intracuff volume of 40 ml \[1\].

Oxygen insufflation at 10–15 L/min using our described technique is highly unlikely to cause gastric insufflation. Firstly, oxygen insufflation at the entrance of the proximal end of the SAD ventilation port can be considered to be in an open circuit. Any buildup of pressure would dissipate quickly via the path of least resistance (retrograde to the atmosphere) rather than moving anterograde through the ventilation port occupied by the bronchoscope. Secondly, 50 L/min of high-flow nasal oxygen only achieves a mean airway pressure of up to 7 cmH\textsubscript{2}O \[2\], which would not overcome a resting lower esophageal sphincter pressure of 15–35 mmHg (20–47 cmH\textsubscript{2}O) \[3\] to cause gastric insufflation. Awake insertion of SADs does not alter the gastroesophageal barrier pressure \[4\]. The following two studies evaluating gastric insufflation with antral ultrasonography also supported a low risk of gastric insufflation. First, face mask ventilation at 10 cmH\textsubscript{2}O under anesthesia without neuromuscular blockade showed that gastric insufflation occurred in 0% of cases \[5\]. Second, all 30 fasted patients who were administered with high-flow nasal oxygen at 70 L/min for a total of 30 min had grade 0 or 1 antrum scores, consistent with fasting. Moreover, in the sitting position, the stomach is lower in relation to the glottis; therefore, the risk of regurgitation and aspiration is potentially reduced.

Conflicts of Interest

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Author Contributions

Patrick Wong (Conceptualization; Supervision; Validation; Writing – original draft; Writing – review & editing)
Wan Yen Lim (Conceptualization; Resources; Validation; Writing – original draft; Writing – review & editing)
ORCID

Patrick Wong, https://orcid.org/0000-0002-3212-9496
Wan Yen Lim, https://orcid.org/0000-0002-0335-0255

References

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When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of KJA will discuss the suspected cases and reach a decision. KJA will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

9-2. Policy of Article withdrawal, retraction, and replacement
1) Article withdrawal
Articles in Press (articles that have been accepted for publication but which have not been formally published and will not yet have the complete volume/issue/page information) that include errors, or are discovered to be accidental duplicates of other published article(s), or are determined to violate our journal publishing ethics guidelines in the view of the editors (such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like), may be “Withdrawn.”
2) Article retraction
Errors serious enough to invalidate a paper’s results and conclusions (Infringements of professional ethical codes, such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like) may require retraction.

3) Article replacement
Replacement (retraction with republication) can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then replacement of the changed paper, with an explanation, allows full correction of the scientific literature.

See also the National Library of Medicine’s policy on retractions and the recommendations of the International Committee of Medical Journal Editors (ICMJE) concerning corrections and retractions, or https://publicationethics.org/resources/guidelines.

9-3. Appeals and complaints
KJA adheres to COPE guidelines regarding appeals to editorial decisions and complaints. For additional information, please visit https://publicationethics.org/core-practices.

Data sharing statement

Manuscript preparation
1. Word processors and format of manuscript
A manuscript must be written in proper and clear English. The manuscript, including tables and their footnotes, and figure legends, must be typed in one double space. Materials should be prepared with a standard 12-point typeface or greater (Times New Roman typeface is preferred). The manuscript should be in the following sequence: cover letter (optional), title page file, manuscript (title and running title, abstract and keywords, introduction, materials and methods, results, discussion, references, tables, and figure legends), figures, other submission elements. All pages should be numbered consecutively starting from the title page. All numbers should be written in Arabic numerals throughout the manuscripts. Our preferred file format is DOCX or DOC. A single PDF file containing all materials in a file including figures and figure legends. In that case, authors should add line numbers throughout the document. Manuscript containing anything in headers and footers, except of page numbers, will be returned to authors. If your PDF submission is accepted, you will be asked to upload your final document file in DOCX or DOC format as well. Make sure to update your PDF file with the most recent version of your manuscript.

2. Abbreviation of terminology
Abbreviations should be avoided as much as possible. When they are used, full expression of the abbreviations following the abbreviated word in parentheses should be given at the first use. Common abbreviations, however, may be used, such as DNA. Abbreviation can be used if it is listed as a MeSH subject heading (http://www.ncbi.nlm.nih.gov/mesh).

3. Word-spacing
1) Leave 1 space for each side, using arithmetic marks as +, −, ×, etc.
Leave no space for hyphen between words.
2) Leave 1 space after “,” and “;”. Leave 2 spaces after “.” and “:”.
3) Using parentheses, leave 1 space each side.
4) Brackets in parentheses, apply square brackets.

4. Citations
1) If a citation has 2 authors, write as “Hirota and Lambert.” If there are more than 3 authors, apply ‘et al.’ at the end of the first author’s surname. Ex) Kim et al. [1].
2) Citation should be applied after the last word or author’s surname.
3) Apply citation before a comma or period.
4) Identify reference by several or coupled Arabic numbers, enclosed in square brackets on the line as [1,3,5].

5. Arrangement of manuscript
ALL articles should be arranged in the following order.
Cover letter (optional)
Title Page file, uploaded separately
Manuscript, as a single file in word processing format (e.g., .doc), consisting of Title and running title, Abstract (if required for the article type; see relevant section), Body Text, References, Tables, Figure Legends, if any (in numerical order, on the same page); be sure to number all pages of the manuscript file. Figures (each Figure should be a separate file in figure file format).

Other submission elements (Supplemental Digital Content, etc.)

Each new section's title should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page. Page numbers should be placed at the middle of the bottom of page. For survey-based clinical studies, the original survey document must be placed at the middle of the bottom of page. For each new section's title should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page. Page numbers should be placed at the middle of the bottom of page. For survey-based clinical studies, the original survey document must be placed at the middle of the bottom of page.

Each new section's title should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page. Page numbers should be placed at the middle of the bottom of page. For survey-based clinical studies, the original survey document must be placed at the middle of the bottom of page. Each new section's title should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page. Page numbers should be placed at the middle of the bottom of page. For survey-based clinical studies, the original survey document must be placed at the middle of the bottom of page.

6. Statistical Analysis

1) Describe the statistical tests employed in the study with enough detail so that readers can reproduce the same results if the original data are available. The name and version of the statistical package should be provided.

2) Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study. Two types of statistical analysis are employed: inferential and descriptive. Inferential analysis is used to test hypotheses about the population based on the sample data, while descriptive analysis is used to summarize and describe the data. Inferential analysis includes hypothesis testing, parameter estimation, and confidence interval estimation. Descriptive analysis includes measures of central tendency, measures of dispersion, and measures of association. The choice of statistical method depends on the type of data and the research question. For example, a t-test is used to compare the means of two independent groups, while a chi-square test is used to compare the proportions of two or more independent groups.

3) The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should describe whether the basic statistical assumptions are met. For example, if the data are normally distributed, a parametric test may be used. If the data are not normally distributed, a nonparametric test may be used.

4) For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality. For example, the Shapiro-Wilk test can be used to test normality.

5) When analyzing a categorical variable, if the number of events and sample is small, exact test or asymptotic method with appropriate adjustments should be used. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and number of events are sufficiently large.

6) The Korean Journal of Anesthesiology (KJA) strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.

7) Except for study designs that require a one-tailed test, for example, non-inferiority trials, the P values should be two-tailed. A P value should be expressed up to three decimal places (not as “P < 0.05”). If the value is less than 0.001, it should be described as “P < 0.001” but never as “P = 0.000.” For large P value greater than 0.1, the values can be rounded off to one decimal place, for example, P = 0.1, P = 0.9.

8) A priori 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. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple comparisons, an adjusted level of significance is acceptable.

9) When reporting a randomized clinical study, a CONSORT-type flow diagram, as well as all the items in the CONSORT checklist, should be included. If limited in terms of the space of the manuscript, this information should be submitted as a separate file along with the manuscript.

10) Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean ± SD of body weight in patients measured on a scale that is accurate to 0.1 kg should be expressed as 65.45 ± 2.52 kg.

11) Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.

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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.

7The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org.
7. Organization of manuscript

1) Clinical or experimental research

(1) Title page
   ① Title
   Title should be concise and precise.
   For the title, only the first letter of the first word should be capitalized.
   ② Author information
   First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.
   ③ Running title
   A running title of no more than 40 characters, including letters and spaces, should be described. If inappropriate, the editorial board may revise it.
   ④ Corresponding Author
   Name, mailing address, phone number, and e-mail address of the corresponding author
   ⑤ Previous presentation in conferences
   Title of the conference, date of presentation, and the location of the conference may be described.
   ⑥ Conflict of interest
   It should be disclosed here according to the statement in the Research and publication ethics regardless of existence of conflict of interest. If the authors have nothing to disclose, please state: “No potential conflict of interest relevant to this article was reported.”
   ⑦ Funding
   Funding to the research should be provided here. Providing a FundRef ID is recommended including the name of the funding agency, country and if available, the number of the grant provided by the funding agency. If the funding agency does not have a FundRef ID, please ask that agency to contact the FundRef registry (e-mail: fundref.registry@crossref.org). Additional detailed policy of FundRef description is available from http://www.crossref.org/fundref/.
   ⑧ Acknowledgments
   Any persons that contributed to the study or the manuscript, but not meeting the requirements of an authorship could be placed here. For mentioning any persons or any organizations in this section, there should be a written permission from them.
   ⑨ IRB number

(2) Manuscript
   ① Title and Running title
   ② Abstract
   All manuscripts should contain a structured abstract that is written only in English. Provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Quotation of references is not available in the abstract. 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
   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 Institutional Review Board 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 de-
termine 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/.

- 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.

- 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], Mg²⁺ [X], Mg²⁺ [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.

- Results
Results should be presented in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all of the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. Citation of tables and figures should be provided as Table 1 and Fig. 1.

- 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 year; volume: start page-final page.


B. Monographs
· If reference page is only 1 page, mark ‘p’.
· Mark if it is beyond the 2nd edition.


C. Chapter

D. Electronic documents

E. Online journal article

F. Papers that have been submitted and accepted for publication should be included in the list, with the phrase ‘in press’ replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction.

・ Type or print each table on a separate sheet of paper.
・ Number tables consecutively in the order of their first citation in the text.
・ Supply a brief title
Tables should be more than 4 rows and should not be over 1 page.
・ Except for titles and first letters, all of the text in the tables should be written in small alphabetic letters.
・ In demographic data, sex would be provided as M/F, and age in yr. Data of year, weight, height, and any other units would be provided with 1 decimal place.
・ “±” sign in the upper column of table should be lined up with the lower column.
・ Footnotes should be provided consecutively in order of the cited tables or statistics.
・ Marks for footnote should be given in order of *, †, ‡, §, II, ¶, **, ††, ‡‡... When marks are used to explain items of the table, indicate them with superscripts.
・ Define all abbreviations except those approved by the International System of Units. Define all abbreviations every time they are repeated.

③ Legends for figures and photographs
· All of the figures and photographs should be described in the text separately.
· The description order is the same as in the footnotes in tables and should be inrecognizable sentences.
· Define all abbreviations every time they are repeated.

③ Figures and illustrations
① The KJA publishes in full color, and encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.
② Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to clearly frame the image. Axis labels should be large enough to be easily readable, and printed in black.
③ Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files. Width of figure should be 84 mm (one column). Contrast of photos or graphs should be at least 600 dpi. Contrast 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).
④ 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.
① In horizontal and vertical legends, the letter of the first En-
English word should be capitalized.
② Connections between numbers should be denoted by “—”,
not “~”. Do not space the numbers (ex. 2–4).
③ Figures (line drawings) should be clearly printed in black
and white.
④ Figures should be explained briefly in the footnotes. The
format is the same as the table format.
⑤ An individual should not be recognizable in the photo-
graphs or X-ray films unless written consent of the subject has
been obtained and is provided at the time of submission.
⑥ Pathological samples should be pictured with a measuring
stick.

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, au-
dio 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., ar-
rows, 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 proce-
dure, 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 re-
view 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 man-
uscript submission and should be marked as supplementary
video files.
① The video clip(s) should have simple file names (e.g., Vide-
o 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, ac-
companied by legends. The video clip file name(s) should re-
fer to the corresponding figure number(s).

2) Case Reports
A case report is almost never a suitable means to describe the
efficacy of a treatment or a drug; instead, an adequately pow-
ered and well-controlled clinical trial should be performed to
demonstrate such efficacy. The only context in which a case re-
port 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 guard-
ian. Authors should submit copies of written informed consents
by using the online manuscript submission system. If it is un-
available, the IRB approval should be needed. Copy of IRB ap-
proval 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 ab-
stract that is written only in English. Provide an abstract of no
more than 150 words. It should contain 3 subsections: Back-
ground, 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 de-
scribe the case and background without a title.
④ Case report: Describe only the clinical statement that is di-
rectly 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 Edito-
rial Board.
⑦ Tables and figures: Proportional to clinical and experimen-
3) 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 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.

4) Letters to the Editor
Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. 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.

5) Book Reviews and Announcements
Book reviews as well as News of Scientific Societies and scientific meeting dates in Korea or abroad can be included. Their formats will be same as Letter to the Editor.

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 November 2019 submissions.