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Core temperature is a critical vital sign that should be monitored throughout the perioperative journey.

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<th>Accuracy</th>
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<tr>
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<td>High</td>
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<td>General Anesthesia</td>
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<td>Medium/High</td>
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<tr>
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<td>Medium</td>
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The Korean Journal of Anesthesiology (Korean J Anesthesiol; KJA) is an international, English-language, and Peerreviewed journal for anesthesiology, critical care, and pain medicine. As an official journal of the Korean Society of Anesthesiologists, KJA was founded in 1968 and published monthly until 2014 and will now publish bimonthly in 2015.

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The journal has been partly supported by the Korean Federation of Science and Technology Societies. KJA is indexed/tracked/covered by ESCI (Emerging Sources Citation Index), KCI (indexed by the National Research Foundation of Korea), PubMed, PubMed Central, EBSCOhost Databases, KoreaMed, KoMCI Web, KoreaMed Synapse, Science Central, SCOPUS, Embase, CAS (Chemical Abstracts Service), WPRIM (Western Pacific Regional Index Medicus), DOI, DOAJ (Directory of Open Access Journal) and Google Scholar. It has been indexed in MEDLINE by U.S. National Library of Medicine. The KCI journals have been seamlessly integrated into the Web of Science since 2014.

Korean Journal of Anesthesiology Volume 73, Number 3, 1 June 2020

The circulation number per issue is 400.

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Indication: Bridion is reversal of neuromuscular blockade induced by rocuronium or vecuronium. 1,3

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* For more information, please refer to the full prescribing information.

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* Before administering BRIDION, please read the full prescribing information.

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Protective ventilation from ICU to operating room: state of art and new horizons

Mikhail Y. Kirov, Vsevolod V. Kuzkov

Department of Anesthesiology and Intensive Care Medicine, Northern State Medical University, Arkhangelsk, Russian Federation

Keywords: Low tidal volume; Patient self-inflicted lung injury; Positive pressure ventilation; Protective ventilation; Ventilation-associated lung injury.
Driving pressure guided ventilation

구동압력에 기반한 인공호흡

Hyun Joo Ahn¹, MiHye Park¹, Jie Ae Kim¹, Mikyung Yang¹, Susie Yoon², Bo Rim Kim², Jae-Hyon Bahk², Young Jun Oh³, Eun-Ho Lee⁴

Department of Anesthesiology and Pain Medicine, ¹Samsung Medical Center Sungkyunkwan University School of Medicine, ²Seoul National University Hospital, Seoul National University College of Medicine, ³Yonsei University College of Medicine, ⁴Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

폐보호 환기 는 현재 널리 사용되는 인공호흡 전략으로 낮은 일회호흡량과 흡기압 및 적절한 호기말양압의 적용으로 이루어진다. 그러나 최근의 여러 후향적 연구에서 일회호흡량, 흡기압, 호기말양압은 환자의 예후와 관련이 없거나, 구동압력(driving pressure)에 영향을 주는 경우에만 관련이 있는 것으로 보고되었다. 따라서, 이번 종설에서는 구동압력의 개념을 소개하고, 특히 수술 후 폐 합병증이 흔하게 발생하는 흉부외과 수술에서의 새로운 인공호흡 전략으로 구동압력에 기반한 인공호흡방법을 소개하고자 한다.

Keywords: Driving pressure; Positive end-expiratory pressure; Postoperative complications; Protective ventilation.
Introducing big data analysis using data from National Health Insurance Service

EunJin Ahn

Department of Anesthesiology and Pain Medicine, Chung-Ang University College of Medicine, Seoul, Korea

Keywords: Cohort; Correlation; Customized research database; Database; Korea; National Health Insurance; Operational definition; Public health service; Sample research database; Statement.
배경: 소아의 경우 내약성 수준이 낮고 여러 약물들이 소아기에 금기이므로, 소아에서의 수술 후 통증은 중요한 문제이다. 본 연구의 목적은 서혜부 탈장 교정술을 받는 소아에서 수술 후 통증 완화를 위한 부피바카인(bupivacaine) 국소 침윤에 추가한 덱스메데토미딘(dexmedetomidine)의 효과를 비교하는 것이었다.

방법: 본 무작위 배정 임상시험에는 이란 시라즈에 소재한 병원에서 단측 헤르니아봉합술을 받은 생후 6-72개월의 소아 60명이 포함되었다. 시험 대상자는 각 군에 30명씩 2개 군에 무작위로 배정되었다. BD 군에서는 군 수술 전 절개 부위에 0.5% 부피바카인 0.2 ml/kg 침윤에 더하여 1 µg/kg 덱스메데토미딘이 투여받았고, BO 군은 부피바카인과 생리식염수를 투여 받았다. 수술 후 4시간 동안 진통제 요구량, 회복시간, 오심/구토, 수술 후 통증 및 진정 점수를 평가하였다. 심박수(HR), 수축기 혈압(SBP) 및 산소포화도(SaO₂)를 주사 전, 주사 후 10분 및 20분에 측정하였다.

결과: 각 군의 80%가 남아있고, 평균 연령은 22.75 ± 18.63개월이었다. SaO₂와 SBP는 군간 차이가 없었던 반면, 10분과 20분 후 BD 군에서 HR이 유의하게 낮았(P < 0.05). BD 군은 수술 1시간 및 2시간 후 통증 점수가 더 낮았고, 처음 3번의 시간 구간에서 진정 점수가 더 높았고, BO 군의 경우보다 회복시간이 더 길었다(P < 0.001).

결론: 탈장교정술을 받는 소아에서 부피바카인의 국소 침윤에 덱스메데토미딘이 추가하는 경우 수술 후 통증이 유의하게 감소하였으며, 진정이 증가하였다.

Keywords: Bupivacaine; Child; Dexmedetomidine; Herniorrhaphy; Pain, Postoperative; Vital signs.
Association of trainee involvement in an acute pain service with postoperative opioid use in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy


Departments of Anesthesiology, Division of Regional Anesthesia and Acute Pain, Medicine, Division of Biomedical Informatics, University of California, San Diego, La Jolla, CA, USA

Keywords: Acute pain service; Epidural; Opioids; Trainee.
Whole-blood hypocoagulable profile correlates with a greater risk of death within 28 days in patients with severe sepsis

전혈 응고저하 장애와 중증 패혈증 환자의 28일 사망 위험률 증가와의 관련성

Annalisa Boscolo¹, Luca Spiezia², Elena Campello², Diana Bertini¹, Vittorio Lucchetta¹, Eleonora Piasentini¹, Alessandro De Cassai², Paolo Simioni²

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²Thrombotic and Hemorrhagic Diseases Unit, Department of Medicine, Padova University Hospital, Padua, Italy

배경: 응고저하 및 혈소판 기능 장애는 패혈증에서의 사망 위험 증가와 관련이 있다. 이 코호트 연구의 목적은 진단 후 29-90일에 사망한 환자와 비교하여 진단 후 28일 이내에 사망한 패혈증 환자에서 패혈증으로 유발된 응고저하 및 혈소판 기능장애(각각 ROTEM® 및 MULTIPLATE®로 평가)가 증가하는지 여부를 확인하는 것이었다.

방법: 2015년 3월부터 2018년 3월까지 Padova University Hospital에 중증 패혈증으로 연속적으로 입원한 환자를 대상으로 하였다. ROTEM® 및 MULTIPLATE® 변수들을 측정하기 위해 모든 환자들로부터 혈액 검체를 채취하였다. 등록된 각 환자를 90일간 추적 관찰하고 사망률을 기록하였다.

결과: 120명의 환자 중, 36명(30%)이 진단 후 28일 이내에 사망했으며(A군), 23명(19%)은 진단 후 29-90일에 사망했고(B군), 61명(51%)은 90일 후 생존했다(생존자). ROTEM® 검사에서의 응고시간과 EXTEM 검사에서의 혈전 형성 시간은 A군이 B군보다 유의하게 길었다. 두 군 모두 EXTEM 검사에서 생존자들보다 유의하게 높은 응고저하를 보였다. MULTIPLATE® 혈소판 기능 분석에서 B군보다 A군에서 유의한 혈소판 기능 저하가 관찰되었다.

결론: 본 연구에서 혈전탄성측정법(ROTEM®)과 응집감출법(MULTIPLATE®)의 병합 사용이 단기 사망 위험에 높은 패혈증 환자를 파악하는 데 도움이 될 수 있다. 이 연구 결과를 확인하기 위해서는 보다 대규모의 연구가 필요하다.

Keywords: Coagulopathy; Hypocoagulability; MULTIPLATE; ROTEM; Severe sepsis; Thrombelastography.
A novel approach to bedside pretransfusion identity check of blood and its components: the Sandesh Positive-Negative protocol

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Keywords: Blood component transfusion; Blood safety; Errors; Hemovigilance; Mistransfusion; Novel intervention; Organization and administration; Prevention and control; Standards.

배경: 혈액제제의 수혈오류는 예방 가능한 사무상의 오류, 특히 수혈 전 침상에서 수혈자의 신원 및 혈액제제 확인 과정의 오류에 일반적으로 기인한다. 따라서, 수혈자와 수혈 혈액의 확인을 위한 표준 장치로 바코드 스캐너 등의 전자 기기 권장된다. 그러나 저개발 국가의 여러 의료시설에서는 이러한 장치의 구입 여력이 없으므로, 보통 수혈자와 수혈 혈액의 확인에 주관적인 육안 평가를 실시한다. 이러한 평가 유형에서는 임상적 오류가 발생하기 쉽다. 따라서, 수혈 전 확인을 하는 새로운 객관적 방법인 'Sandesh Positive-Negative (SPON) 프로토콜'이 개발되었다.

방법: 수혈을 실시하는 75명의 의료진을 대상으로 침상에서의 수혈 전 수혈자와 수혈 혈액의 확인에 대한 비무작위배정 연구를 실시했다. SPON 프로토콜의 경우 수혈 직전 침상에서 맞춤형 혈액 성분 음성 라벨과 같은 환자의 양성 라벨을 일치시키 적합성을 확인한다.

결과: 전체적으로 시행대상자의 85.3%가 기존 표준 관행에 기초하여 수혈 전 신원 확인을 하는 동안 불안을 느꼈다. SPON 프로토콜 시행 후에는 38.7%만이 경증, 중등도 또는 중증 불안을 경험했다. 전체적인 만족 수준 역시 8.0%에서 38.7%로 증가하였으며, 만족하지 못한 경우는 없었다. 기존 관행에 대해 불만족한 경우가 9.3%에 불과하다는 하지만 대략 70.7%가 수술/추가적인 프로토콜에 대한 필요를 느꼈다. 실제 수혈에서 사무적 오류는 관찰되지 않았다.

결론: SPON 프로토콜은 혈액성분에 대한 최종 침상 동일성 확인을 할 때 불안을 줄이고 만족 수준을 증가시키는 비용이 효율적인 객관적 방법이다.
Effects of different sugammadex doses on the train of four ratio recovery progression during rocuronium induced neuromuscular blockade in the rat phrenic nerve hemidiaphragm

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배경: 이 연구에서는 생체 외 모델을 사용하여 다양한 슈가마덱스(sugammadex) 농도에서 로쿠로늄(rocuronium)으로 유도된 신경근 차단으로부터의 회복 중 사연속자극비(train-of-four, TOF)와 TOF의 첫 번째 수축장력(T1) 모두의 회복 패턴을 조사하고 그 관계를 확인하였다.

방법: 60 마리의 adult Sprague-Dawley rat으로부터 횡격막 신경-편측 횡경막의 조직 검체를 채취하였다. 각 검체를 Krebs 완충용액을 채운 기관 욕조(organ bath)에 담고 20초 간격으로 간접적인 최고 자극을 사용한 TOF 패턴으로 자극하였다. 30분의 안정화 기간 후, 각 검체에서 T1의 >95% 억제가 확인될 때까지 로쿠로늄의 부하 용량 및 추가 용량을 연속적으로 투여했다. 검체를 대조군(휴약) 또는 5개 슈가마덱스 농도군(각각 SGX0.75, SGX1, SGX2, SGX4 및 SGX8) 중 하나에 무작위로 배정되었다. 회복 시까지 T1 및 TOF 비를 동시에 사용하여 신경근 차단으로부터의 회복을 관찰하였다.

결과: SGX2와 SGX4군 사이를 제외하고, T1과 TOF 비의 회복 패턴 사이에서 통계적으로 유의한 근간 차이가 관찰되었다(TOFR, P < 0.050). TOFR/T1 값은 대조군, SGX0.75 및 SGX1 군에서 거의 1로 유지되었다. 그러나 이는 SGX2, SGX4, SGX8 군에서 지속적으로 감소되었다. 결론: TOF 비의 회복은 슈가마덱스 용량의 영향을 받을 수 있으며, 로쿠로늄의 용량을 초과하여 슈가마덱스가 투여되는 경우, T1이 완전히 회복되기 전에 TOF 비 1.0에 도달할 수 있다.

Keywords: Acetylcholine; Neuromuscular blockade; Neuromuscular blocking agent; Neuromuscular physiology; Rocuronium; Sugammadex.
Neurolytic abdominal wall blocks with alcohol for intractable gastrostomy site pain in a cancer patient -a case report-

Amnhan’si’si wiby buiby segyegi nangjicjung tebedeuteunhane dukekkbopwiryeonggugun

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배경: 악성 중양의 복벽 전이로 유발된 만성 복통의 치료를 위해 알코올 또는 폐놀과 같은 제제를 사용한 복횡근면(transversus abdominis plane, TAP) 신경파괴술이 보고되어 왔다. 그러나 현재까지 암 환자의 비암성 통증을 위한 신경파괴술에 대한 보고는 없었다.

증례: 본 연구에서는 위루 부위에 지속적인 난치성 통증이 있는 식도암 환자에서 에탄올을 사용하여 늑골하 복횡근면(subcostal TAP) 신경파괴술을 실시하였다. 신경파괴술 이후, 위루 부위 내측 부분을 제외하고 환자의 전체적 통증이 감소했다. 추가로 내측 부위의 지속되는 통증 치료를 위해 에탄올을 사용하여 복직근초(rectus sheath) 신경파괴술을 시행했으며, 신경파괴술의 효과는 4개월 넘게 지속되었다.

결론: 암 환자에게 알코올을 사용한 복횡근면 신경파괴술과 복직근초 신경파괴술은 위루 부위 에 생긴 만성 복벽 통증을 효과적으로 조절하였다.

Keywords: Abdominal wall pain; Cancer pain; Neurolytic peripheral block; Rectus sheath block; Regional anesthesia; Transversus abdominis plane block.
Seroconversion of red blood cell antibody in ABO-incompatible living donor liver transplantation
-a case report-

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Keywords: Erythrocytes; Liver transplantation; Plasmapheresis; Red blood cell antibody screen test; Rituximab.

Case Report
https://doi.org/10.4097/kja.19141
pISSN 2005–6419 • eISSN 2005–7563

Received: April 7, 2019
Revised: June 26, 2019
Accepted: July 3, 2019

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ABO 부적합 생체 간 이식에서 적혈구 항체의 혈청 전환

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배경: 간 이식 수술 중에는 수혈 빈도가 높으며, 용혈 반응을 방지하기 위해 적혈구(RBC) 항체 선별검사가 선행된다. ABO 적합 이식편이 부족하여, 탈감작 및 ABO 부적합 생체간이식 (ABO-i LDLT)이 대체 치료로 대두되고 있다. 탈감작을 위해 수술 전 정맥내 리투시맙(rituximab) 투여 및 혈장교환을 시행한다.

증례: 60세 여성이 B형 간염 바이러스 관련 간세포암종으로 진단받아 ABO-i LDLT가 계획되었다. 이 환자는 2년 동안 RBC 항체 선별검사에서 양성이었으나 수술 전 탈감작 후 검사에서 음성이었다. 마취 후 주 혈청전환이 확인되어 적합한 동축 RBC 준비에 시간이 필요했으며 수술 시작 지연이 불가피했다.

결론: 면역억제 후 마지막 RBC 항체 선별검사가 음성이라도, 임상의는 보다 안전한 치료 및 관리를 위해 이전의 양성 가능성을 고려해야 한다.

Keywords: Erythrocytes; Liver transplantation; Plasmapheresis; Red blood cell antibody screen test; Rituximab.
Sepsis is a life-threatening medical emergency in which extreme immune response is produced against an infection. Only the initiation of prompt and appropriate treatment can lower the mortality rate of sepsis. Although the mechanism underlying coagulation abnormality caused by sepsis has not been clarified, the proinflammatory response of sepsis activates the coagulation system and simultaneously suppresses anticoagulation and fibrinolysis, indicating various clinical aspects of coagulation disorders, ranging from microvascular thrombosis to disseminated intravascular coagulation [1]. Platelets are a cellular mediator of thrombosis and play a pivotal role in coagulation. Recently, many studies have proved that platelets play a role in immunity and inflammation [2]. Conventional clinical tests for coagulation include the platelet count, international normalized ratio (INR), prothrombin time, and activated thromboplastin time. Therefore, many studies have been conducted on the relationship between coagulation tests and the diagnosis of sepsis. INR moderates the predictive values for the diagnosis and prognosis of severe sepsis, such as procalcitonin, interleukin, and C-reactive protein, which are used as biomarkers of sepsis [3]. These findings have increased the possibility of coagulation tests playing a role in predicting the prognosis as a biomarker of the inflammatory process and sepsis. In the June 2020 issue of the Korean Journal of Anesthesiology, Boscolo et al. [4] reported an association between sepsis-induced hypocoagulability and early mortality. They compared the mortality rates up to the first 28 days and from 29 to 90 days of sepsis in terms of hypocoagulability, using point-of-care (POC) coagulation tests, such as ROTEM® (Tem International GmbH, Germany) thromboelastometry or MULTIPLATE® (Roche Diagnostics GmbH, Germany) impedance aggregation between non-survivor groups. In the present study, the samples of the early non-survivors showed higher tendency to hypocoagulate in POC coagulation tests than those of the late non-survivors. However, more studies are needed to reveal the correlation between POC coagulation tests and sepsis-related mortality.

ROTEM® thromboelastometry is a hemostatic test that measures the shear elasticity and dynamics of clot formation and the strength and stability of clots. It is widely used in cardiac and transplant surgeries and trauma cases. MULTIPLATE® is a platelet function analyzer based on impedance aggregation using whole blood. The principle of MULTIPLATE® is to measure the increased impedance of platelets aggregated on metal electrodes. It predicts early mortality or stent thrombosis after percutaneous coronary intervention in cardiology [5] and stent thrombosis and adverse events in neuroradiology [6].

Unlike traditional coagulation tests, which are laboratory-based and require preanalytical processes, such as centrifugation of blood samples, these POC coagulation tests have the advantage of providing results of sepsis-induced coagulopathy as quickly as possible and to continuously observe its trend. In addition, the conventional coagulation test measures only the final stage of coagulation while thromboelastometry has the advantage of differentiating and diagnosing which is the problem process during the initiation of the
clot formation, clot firmness, and fibrinolysis. Since early diagnosis and treatment initiation are the most important management guidelines for sepsis, we look forward to the discovery of a POC test that can easily and quickly predict the progress of sepsis bedside.

**Conflicts of Interest**

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

**References**

The prevention of ventilator-associated lung injury (VALI) and postoperative pulmonary complications (PPC) is of paramount importance for improving outcomes both in the operating room and in the intensive care unit (ICU). Protective respiratory support includes a wide spectrum of interventions to decrease pulmonary stress–strain injuries. The motto 'low tidal volume for all' should become routine, both during major surgery and in the ICU, while application of a high positive end-expiratory pressure (PEEP) strategy and of alveolar recruitment maneuvers requires a personalized approach and warrants further investigation. Patient self-inflicted lung injury is an important type of VALI, which should be diagnosed and mitigated at the early stage, during restoration of spontaneous breathing.

This narrative review highlights the strategies used for protective positive pressure ventilation. The emerging concepts of damaging energy and power, as well as pathways to personalization of the respiratory settings, are discussed in detail. In the future, individualized approaches to protective ventilation may involve multiple respiratory settings extending beyond low tidal volume and PEEP, implemented in parallel with quantifying the risk of VALI and PPC.

**Keywords:** Low tidal volume; Patient self-inflicted lung injury; Positive pressure ventilation; Protective ventilation; Ventilation-associated lung injury.

**Introduction**

Positive pressure ventilation (PPV) is one of the key methods in critical care medicine for maintaining gas exchange and providing an opportunity for recovery from direct or indirect pulmonary injury. Additionally, controlled PPV is required in many surgical interventions conducted under general anesthesia. In both perioperative settings and severe acute respiratory distress syndrome (ARDS), ventilation is associated with neuromuscular blockade and allows precise control of respiratory parameters and gas exchange. However, similar to many other invasive techniques, ventilation can be accompanied by both pulmonary and extrapulmonary complications and is associated with life-threatening respiratory events and remote organ dysfunction.

The problem of ventilator-associated lung injury (VALI) emerged in the previous century and remains a challenge in the new millennium. At this time, we are convinced that the PPV settings should be personalized to protect against VALI arising from the potentially injuring power of the patient–respirator interaction. Furthermore, all patients requiring protective ventilation can be formally divided into subsets depending on the type of prophylaxis: primary and secondary (for perioperative period or intensive care unit.
ICU patients with intact lungs) and tertiary and quaternary (for ICU patients with hypoxemia, mostly due to ARDS) (Fig. 1).

Only a few major evidence-based interventions can be strongly recommended to prevent VALI in ARDS cases and improve survival. These are low tidal volume ($V_t$) ventilation, neuromuscular blockade, and prone positioning [1,2]. In fact, in 2020 we can only guide evidence-based critical care based on 27 multicenter randomized controlled trials that have demonstrated improved ICU survival, of which at least five (almost 20%) involve protective ventilation approaches [2]. In perioperative settings and in ICU patients with intact lungs, only low $V_t$ ventilation is suggested as a means to produce any substantial benefits [3–5]. Until now, the search for the ‘holy grail’ of the truly personalized PPV settings continues, and the existing body of evidence is somewhat contradictory. The novel concept of ventilation energy and power opens new avenues of exploration, which involves the improvement of multiple respiratory determinants [6,7]. Therefore, many categories of both ICU and surgical patients may benefit from precise and personalized respiratory support, supported by new principles (Fig. 2) [8,9].

**Biophysics of ventilator-associated lung injury**

Four well-recognized mechanisms of VALI involve volumo-trauma, barotrauma, atelectotrauma, and biotrauma; however, new insights are proposed reconsidering complications related to mechanical ventilation, including adverse cardiopulmonary interactions, shear injury at the borderline of aerated and atelectatic tissue, lung deflation injury, and effort-induced or patient self-inflicted lung injury (P-SILI) (Table 1) [10–12].

Stress and strain are the key characteristics of every physical material, including lung tissue. Thus, the concept of parenchymal stress and strain is an important part of the modern theory of VALI biophysics [13,14].

**LEVEL OF PREVENTION**

**TARGETS & GOALS**

**EXAMPLES**

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**Fig. 1.** Levels, targets, and intervention strategies for prevention of PPC and ventilator-associated lung injury.

The prophylaxis of negative effects of mechanical ventilation includes four definitive levels: primary, secondary, tertiary, and quaternary. The primary prophylaxis should prevent PPC and VALI before they ever occur by preoperative correction of comorbidities and modification of factors predisposing patients to complications, including ventilation itself (i.e., regional anesthesia). The goal of secondary prevention is to limit the negative impact of intraoperative mechanical ventilation when it has already been started. The tertiary prophylaxis should attenuate the natural course of PPC or ARDS when they have already developed. Finally, the quaternary prevention aims to provide the most rational therapy by all available means leading to avoidance of highly invasive and/or risky respiratory interventions. OSA: obstructive sleep apnea, COPD: chronic obstructive pulmonary disease, PPC: postoperative pulmonary complications, ARDS: acute respiratory distress syndrome, ICU: intensive care unit, LIPS: lung injury prediction score, ARISCAT: Assess Respiratory Risk in Surgical Patients in Catalonia score, $P_{PEAK}$: peak pressure, PEEP: positive end-expiratory pressure, RR: respiratory rate, F: inspiratory flow, VALI: ventilator-associated lung injury, ECMO: extracorporeal membrane oxygenation.
Stress is defined as an outward mechanical force applied to the alveolar area and can be clinically interpreted and quantified as a ‘pressure’, applying the same physical units. At the bedside, the driving ($P_{\text{DRIE}}$) pressure is calculated as the difference between the plateau pressure ($P_{\text{PLAT}}$) and positive end-expiratory pressure (PEEP), and it can adequately characterize the change in lung stress. Therefore, the clinical equivalent of deforming stress is the product of elastic recoil pressure and transpulmonary pressure ($P_{\text{TP}}$).

Strain characterizes the relative distortion of the shape (size and form) of airways (alveoli) resulting from the force applied and is related to stress via Hooke’s law. This parameter reflects the ratio of $V_T$ to the functional residual capacity (FRC). Strain is directly proportional to the $V_T$, adjusted for body weight and includes a static PEEP-related component and a dynamic tidal component related to inflation pressure, with both components carrying dissipated and undissipated energy.

Simply stated, stress determines the risk of barotrauma and strain is related to volumotrauma, while the most important ‘bridge’ between them is represented by the specific lung elastance. Beyond the stress–strain interplay, it is important to recognize any dynamic (cycled) injury due to the dynamic energy load applied to the specific (functional) lung volume and static strain or static energy load. The dynamic energy load is proportional to the ratio of $V_T$ and FRC, while the static energy load is related to PEEP and PEEP-induced changes in volume ($V_{PEP}$) [14,15] (Fig. 3, Table 2).

Under the real conditions of manually adjusted ventilator settings, the inspiratory flow will affect the strain rate, changes in $V_T$ will modify the strain amplitude, and pressures such as $P_{PLAT}$ and PEEP will characterize maximum and minimal stress values, respectively. However, neither stress–strain values nor dynamic or static energy loads can be accurately measured at the bedside.

Every positive pressure inspiration delivered by the respirator transfers a certain amount of energy to the respiratory system of the ventilated patient. The work involved should overcome the re-
sistance of the Airways and increase the 'viscoelastic' volumes of the lungs and chest wall. A certain part of the energy is spent to deform the ultrastructure of Cells and the intercellular matrix, and each Breath results in conservation or absorption of some miniscule Portions of energy within lung parenchyma. In other Words, the amount of energy delivered to the lungs during the mechanical inspiration is not equal to the amount returning during the expiration by means of the elastic recoil of the respiratory system. This 'cumulative dissipation' of mechanical energy produces an inflammatory response and heat production that can increase the risk of VALI over time. The amount of energy delivered per unit of time (joules per minute, J/min) is referred to as the mechanical power, and it can be estimated at the bedside using a number of equations, both in assist-control ventilation and, less accurately, in assisted spontaneous breathing.

Until now, the energy-, work-, or power-dependent Concepts have improved our understanding of the constellation of multiple VALI determinants and individual titration of the ventilation setting, opening new perspectives in the prevention of VALI [9,14,16]. Ventilation is expected to transfer potentially injurious energy per each tidal cycle, and its damaging characteristics involve both set or resulting parameters ($V_t$, PEEP, respiratory rate, inspiration to expiration times ($I:E$) ratio, and inspiratory and expiratory peak flow magnitude and shape) and resulting 'patient-specific' or patient-dependent parameters (peak pressure ($P_{PEAK}$), $P_{DRIVE}$, $P_{PLATE}$, $P_{TP}$ etc.) [14,17–19]. The damaging energy can be modified by the spatial mechanical heterogeneity of the lung tissue, viscoelastic properties of edematous tissue, and, finally, restricted specific pulmonary volume (i.e., 'baby lung') [20]. The threshold of VALI is based on multiple patient-specific factors, including baseline activity of lung inflammation (particularly hyperinflammatory and hypoinflammatory ARDS sub-phenotypes), the mechanism of lung injury (direct or indirect), pulmonary blood flow, and respiratory drive. The power ultimately being transferred to the lungs and eventually resulting in VALI is dependent on the magnitude of the damaging energy and on its exposition time related to the volume and duration of mechanical ventilation [14,16,17]. The proposed upper limit of safe mechanical power varies between 12 J/min and 17 J/min [7,21].

Therefore, beyond $V_t$, many respiratory settings can be directly or indirectly involved in the development of VALI: flow magnitude and shape, respiratory rate, PEEP ($I:E$) ratio, and type of triggering [9,14,17]. The monitoring of resulting pressures, volumes, and mechanical lung properties (compliance) is paramount for assessing the risk of VALI. The safe parameters for protective ventilation are presented in Table 3 and Fig. 3.

### Protective ventilation in ARDS

Low protective and ultra-protective $V_t$ are the key Components in the concept of PPV, both during surgery and in the ICU [4,5,10,22]. Indeed, $V_t$ is a determinant of the interplay between

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**Table 1. Key Mechanisms and Definitions of Ventilator-associated Lung Injury**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Mechanism</th>
<th>Process</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volutrauma</td>
<td>Stretch-induced cyclic or static injury</td>
<td>Excessive $V_t$ of the restricted pulmonary tissue ('baby lung') Inflammation</td>
<td>Low protective $V_t$ (6 ± 2 ml/kg PBW) or ultraprotective $V_t$ (3–4 ml/kg PBW) Neuromuscular blockade and prone positioning in moderate-to-severe ARDS Personalized PEEP</td>
</tr>
<tr>
<td>P-SILI</td>
<td>Vigorous spontaneous effort-induced lung injury</td>
<td>Vigorous diaphragmatic efforts with wide pleural pressure swings due to asynchrony and/or increased respiratory drive</td>
<td>Higher PEEP levels to suppress asynchrony Sedation, neuromuscular blockade, correction of acidosis, suppressing asynchrony and excessive respiratory drive</td>
</tr>
<tr>
<td>Barotrauma</td>
<td>Stress-induced cyclic or static injury</td>
<td>Alveolar and small airways micro- or macro-tears and extra-alveolar gas leakage</td>
<td>Lower airway pressures $P_{PLAT}$, $P_{DRIVE}$, $P_{PEAK}$ and PEEP to avoid over-distension of aerated parenchyma</td>
</tr>
<tr>
<td>Atelectotrauma</td>
<td>Cyclic lung deflation injury</td>
<td>Abrupt disconnections, Low PEEP (?), Pulmonary edema</td>
<td>Avoidance of disconnections, correction of pulmonary edema, personalized PEEP</td>
</tr>
<tr>
<td>Biotrauma</td>
<td>Involvement of extrapulmonary pathways due to primary VALI</td>
<td>Multiple organ failure High proinflammatory cytokines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adverse cardiopulmonary interactions</td>
<td>Low $V_t$ and limitation of damaging power Personalized PEEP to suppress P-SILI</td>
</tr>
</tbody>
</table>

stress and strain (i.e., force/power) applied to restricted functional lung tissue volume. Therefore, along with airway pressures, $V_T$ is a surrogate of pulmonary stress and strain characteristics. The latter are important determinants of VALI associated with the energy or power delivered by a ventilator or created by the spontaneously breathing patient [13,23].

ARDS is associated with atelectases and protein-rich edema resulting from the spatial heterogeneity of the mechanical proper-

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**Fig. 3.** Concept of energy in ventilator-associated lung injury (A) and proposed protective ventilation settings (B). Panel A demonstrates the characteristics of the tidal cycle associated with VALI and potentially injurious mechanical energy delivered, accumulated, and ‘dissipated’ over the respiratory system. During constant inspiratory flow and assist-control ventilation, the sum of the total PEEP driving pressure, and flow-resistive pressure represents the total inflation or ‘peak’ pressure. The total tidal inspiratory energy (power) consists of three potentially injurious and adjustable components: PEEP-related, total elastic, and flow-resistive tidal energies. The elastic energy dissipates during expiration through both pulmonary tissue (cell deformation and heat) and through the circuit and valves of the respirator. Panel B provides an overview of thresholds and interventions to prevent VALI, including low tidal volume, limited peak, plateau, and PEEP, respiratory rate, duration of tidal cycle, flow profile, and inflation power. $P_{res}$: flow-resistive pressure, $P_{peak}$: peak pressure, $P_{plateau}$: plateau (pause) pressure, $P_{drive}$: driving pressure, PEEP: intrinsic (auto-) positive end-expiratory pressure, PEEP$_e$: extrinsic (set) positive end-expiratory pressure, $I:E$: ratio of inspiration to expiration times, $P_{infl}$: total inflation pressure, $F$: flow, $R$: resistance, $V_T$: tidal volume, $C$: compliance, $E$: energy, PBW: predicted body weight.
ties of the lungs, notably compliance. The reduction of well-aerated volume of functional pulmonary tissue surrounded or mixed with collapsed, surfactant deficient, or flooded alveoli has been widely recognized as a ‘baby lung’ phenomenon [20]. However, the true value of a safe $V_T$ is personal and is determined by the functional (residual or specific) lung volume and regional mechanics [10]. Owing to the dramatically reduced volume of aerated functional lung parenchyma, even a low $V_T$ can be injurious in some lung areas, causing severe overdistension of the alveoli while the compliance remains relatively unchanged.

Prone positioning is an effective approach to increase the functional pulmonary volume by reopening the gravity-dependent dorsal atelectatic areas, reducing ventilation-perfusion mismatch, and increasing the aeration homogeneity. To improve survival in ARDS, the exposure to prone positioning requires at least 12–16 h. Notably, prone positioning is commonly applied in parallel with sedation and neuromuscular blockade in moderate-to-severe ARDS patients [24,25].

Neuromuscular blockade has the clear potential to reduce VALI, as it guarantees precise low $V_T$ settings and can reduce bio-trauma via the direct anti-inflammatory effects of muscular relaxants [26]. However, this approach for prevention of VALI is controversial and can increase the risk of serious adverse events, namely, ICU-acquired weakness, diaphragm disuse atrophy, prolonged ICU stay, ventilator dependency, and hemodynamic instability associated with deep sedation [27]. Despite these negative effects, in cases involving severe ARDS and ventilator asynchrony, resulting in excessively high $V_T$ and P-SILI, neuromuscular blockade prevents any spontaneous breathing activity and can be beneficial when it is not possible to synchronize the patient to a ventilator using adjustment of respiratory parameters or conventional sedation techniques.

Patient self-inflicted lung injury

Early restoration of spontaneous breathing activity can bring potential benefits, including improved gas exchange, reduced requirements in sedation, and prevention of diaphragm atrophy and ICU-acquired polynucleomyopathy. However, both experimental

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**Table 2. Key Definitions of the Physical Mechanisms of Ventilator-associated Lung Injury**

<table>
<thead>
<tr>
<th>Value</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>Force (pressure) applied to alveoli, resulting in change of their resting condition ($P_{TP}$)</td>
</tr>
<tr>
<td>Strain</td>
<td>Dynamic ($V_T$) or static (end-expiratory lung volume) distortion of the alveoli or change in volume resulting from stress</td>
</tr>
<tr>
<td>Energy/work</td>
<td>Work during breathing: $P \Delta V$ / $P$ / $A$ / $L$</td>
</tr>
<tr>
<td>Power</td>
<td>Energy applied per unit of time (tidal energy / RR)</td>
</tr>
<tr>
<td>Injury threshold</td>
<td>The level of specific stress–strain associated with the initiation of VALI</td>
</tr>
</tbody>
</table>


**Table 3. Settings of Positive Pressure Ventilation during Perioperative Period and in ICU Patients without and with ARDS**

<table>
<thead>
<tr>
<th>Settings</th>
<th>Perioperative patients</th>
<th>Subgroup</th>
<th>ICU patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_T$ (ml/kg PBW)</td>
<td>6–8</td>
<td>6–8</td>
<td>4–8 (3–4)$^*$</td>
</tr>
<tr>
<td>$P_{DRIVE}$ (cmH$_2$O)</td>
<td>≤ 13</td>
<td>≤ 15</td>
<td>≤ 10 (!)</td>
</tr>
<tr>
<td>$P_{PLAT}$ (cmH$_2$O)</td>
<td>&lt; 16</td>
<td>&lt; 30</td>
<td>&lt; 27</td>
</tr>
<tr>
<td>RR (/min)</td>
<td>8–18</td>
<td>15–35</td>
<td>5–35</td>
</tr>
<tr>
<td>PEEP (cmH$_2$O)</td>
<td>0–5</td>
<td>5–15</td>
<td>10–24</td>
</tr>
<tr>
<td>SpO$_2$ (%)</td>
<td>92–100</td>
<td>92–97</td>
<td>92–97</td>
</tr>
<tr>
<td>PaCO$_2$ (mmHg)</td>
<td>35–45</td>
<td>35–45</td>
<td>45–70$^*$</td>
</tr>
<tr>
<td>Prone position</td>
<td>Depends on surgery</td>
<td>No</td>
<td>Recommended$^*$</td>
</tr>
<tr>
<td>NMB</td>
<td>Monitored</td>
<td>No</td>
<td>Recommended$^*$</td>
</tr>
</tbody>
</table>

and clinical studies have shown that excessively vigorous spontaneous efforts can lead to aggravation of VALI [28–31]. The risk of a condition coined as P-SILI or effort-induced lung injury is strongly associated with moderate-to-severe ARDS. Typically, P-SILI results from the unsuppressed overcoming of a safe \( V_T \) in cases of high ventilation demand [12,26,32]. The risk of P-SILI is often associated with multiple factors, including excessive ventilator settings, asynchrony, pain, anxiety, delirium and neurologic injury, high metabolic demand and hyperthermia, hypercapnia, and acidosis [22,33]. A systemic inflammatory response can trigger most of these conditions, resulting in increased respiratory drive and a compromised Hering–Breuer reflex to depress tidal pulmonary stretch [34]. A too vigorous respiratory drive due to patient respiratory efforts and excessive \( P_{IP} \) will result in global and local overdistension of lung tissue [30,33]. Thus, there are three primary mechanisms associated with P-SILI: pulmonary overdistension, increased lung blood flow, and patient ventilator asynchrony (double and reverse triggering) [31].

Excessive respiratory efforts are difficult to control, while volume-controlled PPV is not capable of preventing P-SILI in ARDS [35]. In 2019, Moss et al. [27] (the ROSE trial) demonstrated that application of a higher PEEP strategy using light sedation vs. neuromuscular blockade and deep sedation can maintain safe spontaneous breathing and does not result in either barotrauma or in increased 90-day mortality. In fact, a higher PEEP level in moderate-to-severe ARDS cases suppresses lung inflammation; decreases diaphragmatic activity, gradient of pleural pressure, and lung distension and stress; improves gas exchange; and prevents the development of P-SILI [35,36].

**Advantages of low tidal volumes and controversy regarding positive end-expiratory pressure**

**Low tidal volume**

No doubt that ventilation with low \( V_T \) is a cornerstone of the current approach to lung protection. It can prevent VALI in a variety of clinical scenarios, including patients manifesting ARDS, ICU patients without ARDS, and in perioperative surgical settings. Despite potential worsening of oxygenation, accumulation of \( CO_2 \), and increased sedation requirements, low \( V_T \) decreases the harmful effects of PPV [37]. The key mechanism regarding the protective effect of low \( V_T \) consists of the counteracting trigger factors of VALI: increased dynamic strain (i.e., \( V_T \)) and PEEP-related static strain (FRC). Thus, researchers began to develop a modern profile of protective ventilation by decreasing the \( P_{PLAT} \), considering the open lung approach and permissive hypercapnia [38,39], and then comparing low \( V_T \) to conventional ventilation [37,40]. In 2000, the NIH ARDS Network enrolled 861 patients with ARDS in a randomized trial and showed that in comparison with the ‘traditional’ \( V_T \) of 12 ml/kg and \( P_{PLAT} < 40 \text{cm}^3\text{H}_2\text{O} \), positive pressure ventilation with \( V_T \) of 6 ml/kg and \( P_{PLAT} < 30 \text{cm}^3\text{H}_2\text{O} \) resulted in a striking increase in survival rate [37].

Therefore, considering the profound decrease in functional pulmonary volume due to heterogeneity of the lungs in ARDS (i.e., ‘baby lung’) [20], it would seem reasonable to titrate protective \( V_T \) using the true volume of functional lung capacity. However, measuring the functional lung volume is not an easy task. Thus, at the bedside, we can use its surrogate parameters, such as static respiratory compliance and the derived difference between \( P_{PLAT} \) and PEEP (the so-called \( P_{DRIVE} \)). This approach was confirmed by a number of studies showing that \( P_{DRIVE} \) can be more accurate for predicting survival compared to PEEP, \( P_{PLAT} \), and \( V_T \) itself [21,23,41].

Until now, the universal recommendation is to maintain the \( V_T \) at 6 ± 2 ml/kg of the predicted body weight (4–8 ml/kg PBW) in a vast majority of ARDS patients to maintain \( P_{PLAT} \) below 30 cmH\textsubscript{2}O [22,42]. However, ICU practice remains inexplicably far from this standard. The recent LUNG SAFE study has shown that ICU patients with ARDS had \( V_T \) values above 8 ml/kg and 10 ml/kg of PBW in more than 30% and 10% of cases, respectively. In addition, \( P_{PLAT} \) above 30 cmH\textsubscript{2}O was registered in 10% of cases, while \( P_{DRIVE} \) values above 15 cmH\textsubscript{2}O were observed in almost half of the ARDS patients [43].

**Ulralow tidal volume**

In severe ARDS cases, the volume of the functional (aerated) lung parenchyma can fall beyond the size of the ‘baby lung’ of a 6-year-old child [20]. In these settings, even a protective \( V_T \) of 6–8 ml/kg can be excessive, associated with \( P_{DRIVE} \) above 15–19 cmH\textsubscript{2}O [42,44]. Currently, ultralow \( V_T \), referred to as a volume below 6 ml/kg of PBW, may be used. The application of ultralow \( V_T \) ventilation in patients with severe ARDS requires a neuromuscular block and deep sedation to prevent asynchrony and P-SILI; this strategy can also be used during extracorporeal membrane oxygenation to allow the lungs to rest as well as to prevent them from de-aeration and collapse. The recent study of Richard et al. [45] demonstrated that ultraprotective \( V_T \) could be safely set in almost two-third of patients with severe ARDS, which resulted in a mean decrease of 4 cmH\textsubscript{2}O in the \( P_{DRIVE} \) but it was accompanied by transient respiratory acidosis in one-third of patients. Therefore, permissive hypercapnia should be limited to the range of 60–70

https://doi.org/10.4097/kja.19499
mmHg to avoid severe acidosis. Further investigations into this approach are strongly warranted.

**Controversy involving positive end-expiratory pressure**

PEEP is perhaps the most controversial approach used to prevent VALI because its possible benefits for arterial oxygenation should be carefully weighed against potential static lung injury and negative hemodynamic effects [4,16]. The rationales to set the PEEP for prevention of VALI include inflation of consolidated lung areas and improvement of respiratory compliance. Therefore, PEEP has the potential to reduce $P_{\text{D}}$ and achieve low $V_t$ while simultaneously preserving adequate oxygenation by recruiting alveoli and by counteracting atelectrauma [46].

Until now, the optimal PEEP for ARDS patients remains unsettled. It has been shown in several studies that during protective ventilation, PEEP alone does not improve survival [47–50]. The personalized control of PEEP using esophageal monitoring of $P_{\text{a}}$ and a combination of PEEP with alveolar recruitment maneuvers (RM) also have not resulted in any survival benefits [51–53]. In a large meta-analysis, including more than 2000 patients, Briel et al. [54] demonstrated that a high PEEP level could decrease mortality in moderate and severe ARDS cases only [54]. Despite the controversy of these findings compared to a more recent meta-analysis by Walkey et al. [55], the recommendation to use higher PEEP in moderate and severe ARDS is implemented in current international guidelines [42]. Moreover, the ART multicenter study revealed increased mortality after high PEEP and alveolar recruitment in moderate-to-severe ARDS cases [52]. However, the methodology of this study is questionable, as patients were subjected to long-lasting periods of excessive intrathoracic pressures. In a more recent PHARLAP investigation, high PEEP and recruitment did not reduce the duration of ventilation-free days or decrease mortality, but it did decrease the use of new hypoxemic adjuvant therapies for moderate-to-severe ARDS (i.e., inhaled nitric oxide, extracorporeal membrane oxygenation, and prone position) [53].

A triad of high PEEP complications includes hypotension, arrhythmias, and static lung injury, usually manifesting as barotrauma. Thus, despite previous major multicenter trials having shown that high PEEP does not increase the risks of these adverse events compared to low PEEP [47,49], the ART trial demonstrated a three-fold rise in incidences of barotrauma and pneumothorax [52] and the PHARLAP study revealed a two-fold rise in arrhythmia rates using a high PEEP approach [53].

In summary, a high PEEP level (10–24 cmH$_2$O; Table 2) should be considered only for patients with moderate-to-severe ARDS with low risk of arrhythmias and barotrauma in parallel with thorough hemodynamic and respiratory monitoring. Increased PEEP can also be useful to reduce the risk of P-SILI and avoid the need for neuromuscular blockade [27,31]. The increase in PEEP should be titrated and gradual (by 2 cmH$_2$O per several minutes) and should not result in $V_t$ exceeding 8 ml/kg, $P_{\text{a}}$ above 30 cmH$_2$O, and $P_{\text{D}}$ above 15 cmH$_2$O [1,47]. Personalization of PEEP settings to attenuate VALI can also include the assessment of $P_{\text{a}}$ intraabdominal pressure, and dead space volume [51,56] (Table 3).

**Additional evidence-based protective interventions**

Evidence-based interventions in ARDS patients with high risk of VALI are not limited exclusively to low $V_t$. ‘Adjuvant’ therapies, including prone positioning and/or neuromuscular blockade have substantial potential for improving outcomes in ARDS. However, it is important to remember that any lung protective intervention should not increase the risk of extrapulmonary life-threatening complications.

**Prone position**

Prone positioning was introduced into ICU practice 50 years ago to counteract severe hypoxemia in mechanically ventilated patients. In contrast to the supine position, the prone position changes the vertical gradient of intrapleural pressure and decreases stress in posterior lung regions. In addition, the prone position attenuates the influence of intrathoracic and intraabdominal pressures on lower portions of pulmonary tissue, thus increasing effective lung volume and compliance. As pulmonary perfusion persists in dorsal regions, the prone position can change the ventilation-perfusion ratio and dramatically improve arterial oxygenation. Moreover, it predisposes the lungs to the gravitational recruitment of collapsed dorsal regions and increases the homogeneity of lung ventilation. It has been shown that in severe ARDS, the prone position can mitigate VALI by improving the distribution of a specific $V_t$ and pulmonary blood flow and has the potential to improve gas exchange and compliance. In severe ARDS, this technique should be initiated as early as possible and becomes more effective when combined with low $V_t$, higher PEEP, RM, and additive vasodilator therapies (e.g., inhaled nitric oxide) [57–60].

The PROSEVA trial has demonstrated a significant increase in survival in moderate-to-severe ARDS after prone positioning. Neuromuscular blockade was maintained in 85% of the 466 patients enrolled [57]. It is important to emphasize that prone positioning is only beneficial if four criteria are fulfilled: low $V_t$, severe hypoxemia (partial oxygen pressure in arterial blood to inspired oxygen fraction ratio (PaO$_2$/FiO$_2$) less than 100–150 mmHg), ex-
position of 12–16 h per day, and early application [58–60]. Specific risks of prone positioning include endotracheal tube dislodgement and/or occlusion as well as pressure sores on the skin and soft tissues [59]. Therefore, prone positioning for at least 12 h per day can be implemented to mitigate VALI in ARDS patients with refractory hypoxemia and high airway pressures, not responding to neuromuscular blockade, and low or ultralow Vₚ; and requires careful monitoring [25,42].

Neuromuscular blockade

Neuromuscular blockade can decrease the risk of VALI and P-SILI by the suppression of asynchrony, guaranteed maintenance of protective Vₚ, and reduced work and power of spontaneous breathing. In patients with moderate-to-severe ARDS, muscle relaxants (such as cisatracurium) improve oxygenation, may exert a direct anti-inflammatory effect, and have the potential to decrease mortality [26,61]. In 2010, Papazian et al. [26] showed in an ACURASYS randomized study of moderate-to-severe ARDS that neuromuscular blockade and deep sedation for 48 h are associated with improved survival, shorter duration of mechanical ventilation, and reduced incidence of barotrauma. The results were confirmed in the meta-analysis of Alhazzani et al. [61] which included three studies of prolonged cisatracurium infusion, although the more recent ROSE trial did not reveal any survival benefits for patients receiving muscle relaxants [27]. The adverse effects of neuromuscular blockade include ICU-acquired weakness (not reported in the ACURASYS trial), particularly in patients receiving glucocorticoids, and complications associated with deep sedation, including hemodynamic instability [27,61].

Therefore, early neuromuscular blockade should be considered in ARDS patients with refractory hypoxemia (PaO₂/FiO₂ less than 100–150 mmHg) and increased Pplat to guarantee protective Vₚ and to decrease P-SILI only when sedation and respiratory settings are unable to synchronize the patient to a ventilator.

Alveolar recruitment and open lung approach: not for everyone?

Alveolar RM combined with titrated high PEEP settings constitutes the ‘open lung’ concept [48,50]. Successful RM requires the transient increase of airway pressures to re-open collapsed alveoli and, subsequently, to prevent atelectrauma with stepwise adjusted PEEP. In 2016, Pirrone et al. [62] in a prospective intervention study involving medical and surgical ICUs, demonstrated that RM followed by PEEP titration (12 cmH₂O) can improve respiratory mechanics in morbidly obese patients (body mass index > 35 kg/m²) [62]. However, multiple meta-analyses have failed to show substantial survival benefits in patients receiving RM [53,63,64], and the ART trial involving an aggressive methodology of RM even increased mortality [52]. Adverse effects of recruitment are similar to those of high PEEP and, in some cases, can potentially overcome the potential protective effects. These adverse effects can include transient hypotension, decreased cardiac output, arrhythmias, hypoxia, and overdistension of the aerated specific volume, as well as barotrauma (pneumothorax) [52,64,65].

It would appear reasonable to personalize the application of RM to prevent VALI by focusing this approach on patients without hypovolemia, arrhythmias, severe cardiac comorbidities, refractory shock, and risk of barotrauma. The optimal methodology of RM is arguable and, probably, as in the case of PEEP, should be associated with the decrease of both pulmonary pressures and Vₚ; otherwise, despite improved oxygenation, increased pressures can contribute to static lung injury [14]. The conflicts between the potential benefits of RM and high PEEP versus increased risk of ‘static’ lung injury resulting in VALI prompted Pelosi et al. [66] to declare a new striking motto: ‘Close down the lungs and keep them resting’ 25 years after the original concept by Lachmann [67] (1992): ‘Open up the lung and keep the lung open.’ The controversial effects of RM and high PEEP on pulmonary edema and systemic hemodynamics, the evidence of reduced injury and inflammation in the collapsed regions, the risk of static strain and overdistension, and even the emerging concept of ‘permissive atelectases’ support the position that we should personalize an ‘open lung approach’ only to the subsets of responders with significant and proven recruitment potential [68,69].

Personalized approach to VALI prevention in ARDS

In the future, priorities in the prevention of VALI and improvement of outcomes may shift to limiting the injurious power or energy associated with breathing [6–9]. The assessment of lung capacity, heterogeneity of lung injury, pulmonary edema, transpulmonary pressure, and gas exchange are vital requirements for personalized respiratory settings. Attempts to reduce respiratory rate and Vₚ result in a decrease in minute volume and damaging power; however, they can be associated with permissive hypercapnia (PaCO₂ 45–70 mmHg). The damaging effects of excessive spontaneous efforts to breathe can be suppressed by deep sedation and/or neuromuscular blockade and high PEEP to decrease swings in PTP, the work of spontaneous breathing, the response to permissive hypercapnia, and, finally, the risk of P-SILI [26,31]. All determinants of power and energy should be optimized, including...
gradual changes in PEEP (controlled to produce specific \( P_{\text{DRIVE}} \) and \( V_T \)), minute ventilation, respiratory rate, flow magnitude and profile, and the I : E ratio. It has been shown that the I : E ratio. It has been shown that the I : E ratio varying from 1 : 1 to 1.5 : 1 can be associated with decreased inspiratory flow, providing a safer controlled constant flow profile [8,9].

Protective ventilation in ICU patients without ARDS

In contrast to manifesting ARDS, the subset of ICU patients without ARDS requiring positive pressure ventilation can be much more heterogeneous in terms of risk of VALI (Fig. 2). This category of critically ill can be subdivided into patients with intact lungs without common risk factors involving ARDS, intact lungs with some risk factors of ARDS (e.g., septic shock, aspiration) and, finally, other lung disorders and hypoxemia that do not meet ARDS criteria. Although there is no strong consensus concerning lung protective ventilation patterns and settings in this scenario, it has been demonstrated that low \( V_T \) ventilation can prevent VALI in the patients with initially intact lungs, and multiple studies have confirmed the benefits of protective ventilation in patients without ARDS [4,70,71]. A further meta-analysis revealed that the implementation of low \( V_T \) resulted in decreased risk of pulmonary complications, including atelectases and pneumonia, reduced ICU and hospital length of stay, and increased number of ventilator-free days, but did not influence the survival rate [72]. Therefore, in this subset of ICU patients, low \( V_T \) is prudent, safe, and is associated with better outcomes [73,74]. Furthermore, use of a high PEEP level is more controversial and should perhaps be used only in situations where the risk of P-SILI exists, when it can decrease \( V_T \) to normal values and attenuate static strain injury [15, 30,31].

Protective ventilation during perioperative period

Annually, more than 310 million surgical interventions are performed and most require general anesthesia with neuromuscular blockade and positive pressure ventilation [75,76]. Many operations last longer than 2–3 h and are accompanied by increased risk of respiratory complications (Fig. 2). Postoperative pulmonary complications (PPC) in patients with intact lungs are quite common (3%–8%) and represent a heterogeneous group of events: atelectases, pulmonary edema, postoperative pneumonia, pleuritis, re-intubation, requirement for postoperative supplemental oxygen, and ARDS [77,78]. It is well-recognized that PPC increase the risk of infectious and surgical complications, length of ICU and hospital stay, healthcare costs, and personnel workload, and are a target for primary and secondary prevention (Fig. 1) [5,79]. The influence of PPC on mortality remains is still not well defined and warrants further analysis [80]. Thus, the problem of PPC requires better understanding among anesthesiologists and the implementation of interventions with proven effects to prevent these complications [81,82].

Although the most common PPC are atelectases, one of the most severe PPC is ARDS, whose cumulative incidence may outweigh the incidence of ‘medical’ ARDS in the ICU. The important determinant of perioperative VALI is volutrauma. Therefore, low \( V_T \) ventilation is of paramount importance to prevent PPC; however, despite its clear advantages, intraoperative protective ventilation is still not widely implemented in current anesthesia practice [83]. There is a wide variety of studies in the different areas of perioperative care showing the benefits of low \( V_T \) for protective ventilation [84–86]. Along with ICU settings, an implementation of lower \( V_T \) and moderate, but not zero-PEEP can dramatically reduce the injurious effects of ventilation during surgery [3,5].

Large-scale studies have been mainly performed on the population of abdominal surgical patients. The IMPROVE trial has shown that ventilation with ‘traditional’ \( V_T \) of 10–12 ml/kg and zero PEEP increases the risk of PPC and prolongs hospital stay compared with a \( V_T \) of 6–8 ml/kg and PEEP of 6–8 cmH\(_2\)O [87]. An extended meta-analysis by Serpa Neto et al. [5] found a close relationship among PPC, incidence of postoperative respiratory failure, and \( V_T \).

Higher levels of PEEP during the perioperative period do not provide any additional benefits [5]. In another study, the PROVHILO trial (2014) demonstrated that a strategy consisting of a high level of PEEP combined with RM during open abdominal surgery does not protect against PPC; the authors conclude that the perioperative protective ventilation strategy should include low \( V_T \) and low PEEP without RM [88]. The recent multicenter PROBESE trial (2019) also demonstrated that setting a high PEEP of 12 cmH\(_2\)O and using RM in obese patients (body mass index > 35 kg/m\(^2\)) is not associated with any reduction of PPC compared to a low level of PEEP (4 cmH\(_2\)O) [89]. The rationale for higher intraoperative PEEP and RM in thoracic surgery with one-lung ventilation is being explored in the ongoing PROTHOR trial (NCT02963025) [90].

Before surgical intervention, patients should be carefully assessed for the risk of PPC using specific scoring systems (LIPS, ARISCAT, and/or SPORE) to personalize a perioperative lung protective strategy [91–93]. The group with high risk of PPC
should prompt targeted management consisting of a bundle of preventive measures that are not limited to ventilation alone. Thus, compared with open abdominal surgery, the risk of respiratory failure, ARDS, pulmonary infections, and pulmonary embolism can be reduced by applying a laparoscopic approach [94]. Perioperative fluid therapy and transfusion can also trigger postoperative ARDS; therefore, a restrictive goal-directed fluid strategy should be considered for patients with high risk of PPC [95,96]. Volatile anesthetics have lung-protective potential and can improve the surgical outcome as well [97]. It appears reasonable to avoid high doses of muscle relaxants and opioids, use selective reversal agents, and give preference to neuraxial methods instead of using general anesthesia [98,99]. Postoperative continuous positive airway pressure, upright positioning and sitting posture, and early mobilization can all reduce the incidence of PPC [100–102].

The consensus approaches for protective ventilation settings in surgical patients are presented in Table 3 and Fig. 2. Note that in the LAS VEGAS study, only the peak pressure (without the plateau or driving pressures) was used as an independent predictor in PPC; however, the P\textsubscript{DRIVE} should also be minimized in the process of PEEP personalization [19,88]. Because high FiO\textsubscript{2} levels during perioperative period can be accompanied by hyperoxia and several undesirable effects, and as robust evidence is lacking indicating a beneficial effect of FiO\textsubscript{2} levels above 60% on surgical site infection, the routine use of an FiO\textsubscript{2} level > 60% during anesthesia and surgery is not recommended [103]. Furthermore, using an FiO\textsubscript{2} level of 80% during pre-and post-oxygenation to prevent atelectases appears to be risky in difficult airways. The potential benefits of decreased respiratory rate, inspiratory flow, and FiO\textsubscript{2} as well as perioperative RM warrant new studies in different subpopulations of surgical patients. During the early postoperative period, automated weaning from mechanical ventilation systems can reduce the number and duration of deviations from the safe ventilation zone, decrease the workload on medical staff, and provide additional protective parameters as compared to conventional modes [104]. Thus, these systems have the potential for further integration in postoperative respiratory care.

Conclusions

Today, protective respiratory support with reduced V\textsubscript{T} and pressures is the gold standard for prevention of VALI and PPC, both in perioperative settings and for ICU patients. We have observed a shift in paradigm from ‘normalizing’ blood gases, early restoration of spontaneous breathing, and the ‘open lung’ approach to a balanced strategy of personalized lung protection based on a set of interventions aiming to limit lung stress and strain. The ‘less is more’ and ‘choosing wisely’ strategies should be implemented by ICU physicians and anesthesiologists in all subsets of ventilated patients by considering individual patient risk, pulmonary comorbidity, risk factors of ARDS, respiratory mechanics, and gas exchange. Finally, the concept of injurious energy load and power can help to reconsider the effects of PEEP and alveolar recruitment.

Conflicts of Interest

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

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Driving pressure guided ventilation

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Protective ventilation is a prevailing ventilatory strategy these days and is comprised of small tidal volume, limited inspiratory pressure, and application of positive end-expiratory pressure (PEEP). However, several retrospective studies recently suggested that tidal volume, inspiratory pressure, and PEEP are not related to patient outcomes, or only related when they influence the driving pressure. Therefore, this review introduces the concept of driving pressure and looks into the possibility of driving pressure-guided ventilation as a new ventilatory strategy, especially in thoracic surgery where postoperative pulmonary complications are common, and thus, lung protection is of utmost importance.

Keywords: Driving pressure; Positive end-expiratory pressure; Postoperative complications; Protective ventilation.

Introduction

Postoperative pulmonary complications are not rare in thoracic surgery due to direct surgical injury of the lung tissues and one lung ventilation which is prone to volutrauma, barotrauma, atelectrauma, and oxygen toxicity [1–3]. In addition, immune cells are abundant on the pulmonary vascular endothelium and alveolus [4], thus, direct and indirect injuries to the lung tissues trigger a profound inflammatory response and increase pulmonary vascular permeability in both dependent and non-dependent lungs [5]. These reactions often precede systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS), and pneumonia [6–8]. Therefore, lung protection is of utmost importance, and protective ventilation is strongly recommended in thoracic surgery [9,10].

The usual settings for protective ventilation during one lung ventilation are tidal volume (VT) 5 to 6 ml/kg of predicted body weight (PBW), positive end-expiratory pressure (PEEP) to 5 cmH₂O and plateau pressure (Pplat) to less than 25 cmH₂O [9–13]. However, a high incidence of postoperative pulmonary complications is still being observed even with a protective ventilatory strategy [3,12,14–16].

Driving pressure was first introduced by Amato et al [17] in 2015 in their meta-analysis study for ARDS patients. The authors suggested that high driving pressure was most strongly associated with worse survival. VT, Pplat and PEEP were not related to patient outcomes, or only related when they influenced the driving pressure. Several retrospective and prospective studies confirmed the importance of driving pressure in ARDS patients [18,19] and surgical patients [12,20–22].

This review article introduces the concept of driving pressure through previous publi-
cations, and will discuss the possibility of driving pressure-guided ventilation as a new ventilatory strategy in surgical patients including thoracic surgery.

**Driving pressure**

**Definition**

Driving pressure is \( P_{\text{plat}} - P_{\text{EEP}} \) and is the pressure required for the alveolar opening [17]. Static lung compliance (Cstat) is expressed as \( \frac{V_T}{(P_{\text{plat}} - P_{\text{EEP}})} \). Thus, driving pressure is also expressed as \( \frac{V_T}{\text{Cstat}} \). Driving pressure has an inverse relationship with Cstat and an orthodromic relationship with \( V_T \) according to this formula. High driving pressure indicates poor lung condition with decreased lung compliance.

\[
\text{Driving pressure} = P_{\text{plat}} - P_{\text{EEP}}
\]

\[
\text{Cstat} = \frac{V_T}{P_{\text{plat}} - P_{\text{EEP}}} = \frac{V_T}{\text{Driving pressure}}
\]

\[
\text{Driving pressure} = \frac{V_T}{\text{Cstat}}
\]

**Retrospective studies for ARDS patients**

Most studies regarding driving pressure were retrospective studies for ARDS patients. Following Amato’s meta-analysis [17], subsequent retrospective studies also showed that driving pressure is more strongly associated with survival than \( V_T \) and PEEP in ARDS patients [18]. Driving pressure was closely related to hospital mortality even among patients who received protective ventilation [19]. The cut-off value of driving pressure for high mortality was approximately 15 cmH\(_2\)O for ARDS patients [17,23], and each unit increase of driving pressure (1 cmH\(_2\)O) was associated with a 5% increment in mortality [18].

High driving pressure was also associated with increased mortality in patients receiving pressure support mode ventilation in a recent retrospective cohort study [24]. The driving pressure was higher in non-survivors than in survivors, but the difference was only 1 cmH\(_2\)O [11 (9 to 14) vs. 10 (8 to 11) cmH\(_2\)O; P = 0.004]. Cstat was lower [40 (30 to 50) vs. 51 (42 to 61) ml/cmH\(_2\)O] in the non-survivors, but peak pressure was not different between non-survivors and survivors [all values median (IQR)]. Lower Cstat [odds ratio, 0.92 (95% CI, 0.88 to 0.96)] and higher driving pressure [odds ratio, 1.34 (95% CI, 1.12 to 1.61)] were independently associated with increased risk of death, but peak inspiratory pressure was not associated with mortality [24].

**Suggested mechanism of how driving pressure guided-ventilation can decrease morbidity**

'Functional lung size' is the volume of aerated lung available for ventilation (Fig. 1) [25]. 'Functional lung size' is derived from the 'baby lung' concept. Computed tomography (CT) examinations showed that the ARDS patients only have the same amount of normally aerated lung tissue as a 5–6 year-old child [25]. The respiratory system compliance is linearly related to the 'baby lung' dimensions. Thus, the ARDS lung is not "stiff" but instead small, with nearly normal intrinsic elasticity. The 'baby lung' concept...
conveys that the \( V_T /'baby lung' \) ratio is more important than the \( V_T /kg \) ratio, and the smaller the 'baby lung', the greater the potential is for ventilation induced lung injury. The 'baby lung' is not a distinct anatomical structure. The CT density redistribution in prone position showed that the 'baby lung' is a functional but not an anatomical concept [25].

Similarly with ARDS, 'functional lung size' would be smaller than expected if the patients have lung pathologies such as atelectasis, consolidation, bullae, effusion, or fibrosis. Either over-distending (barotrauma) or under-ventilating (atelectrauma) the lungs beyond the functional lung size would increase driving pressure [17,25]. Driving pressure would be lowest when the PEEP maintains alveoli at the functional residual capacity at the end of expiration and \( V_T \) expands the lungs within the 'functional lung size' [1,21,26–31]. Fig. 2 shows that ventilation occurring in the high compliance zone shows the lowest driving pressure.

Therefore, driving pressure can be used to guide individualized ventilation based on each patient's functional lung size. Technically, it is easier to use driving pressure as guidance than to use Cstat because driving pressure is the calculation of two simple pressures \( [P_{plat} - PEEP] \) and Cstat is the interaction of pressures and tidal volumes \( [V_T / (P_{plat} - PEEP)] \) which is more difficult to calculate and may show more erratic changes during surgical manipulation than driving pressure.

The two methods to reduce driving pressure

There are no established techniques to reduce driving pressure yet. Driving pressure is dependent on PEEP and \( V_T \) \( [\text{driving pressure} = P_{plat} - PEEP = V_T / Cstat] \). Therefore, adjustment of PEEP and \( V_T \) has the potential to reduce driving pressure. There are few studies regarding PEEP adjustment based on driving pressure [21,30,32] and no studies yet on the \( V_T \) titration based on driving pressure.

PEEP titration

Previously, high PEEP (13 to 15 cmH\(_2\)O) was compared to low PEEP (8 cmH\(_2\)O) in a large scale acute respiratory distress syndrome net (ARDSnet) trial and found no difference in mortality and unassisted breathing \( (n = 549) \) [33]. In a subsequent multicenter randomized controlled trial of 767 adults with acute lung injury, patients were randomly assigned to a moderate PEEP strategy (5–9 cmH\(_2\)O, mean PEEP 7 cmH\(_2\)O) or to a level of PEEP set to reach a \( P_{plat} \) of 28 to 30 cmH\(_2\)O (mean PEEP 15 cmH\(_2\)O). The primary outcome, 28-day mortality rate and the hospital mortality rate were not different between the two groups [34].

According to electrical impedance measurement, each patient and each lung region have different lung compliance [35]. In addition, the majority of patients with chronic obstructive pulmonary disease develop intrinsically variable PEEPs during mechan-
ical ventilation [36]. Therefore, fixed PEEP would be inappropriate regardless of whether it is high or low, and individualized PEEP based on driving pressure may be the next step of protective ventilation. Fig. 3 shows that the same PEEP decreases or increases driving pressure according to the underlying lung pathologies or functional lung size [22,26].

For PEEP titration, most previous studies were small scale studies and PEEP was titrated using Cstat. However, PEEP titration using Cstat also decreased driving pressure. In one study of abdominal surgery patients, PEEP was titrated to yield the highest Cstat (n = 36) in the experimental, or ‘individualized PEEP’ group while the control group received fixed PEEP of 5 cmH\textsubscript{2}O [30]. Individualized PEEP decreased driving pressure by 28% compared to fixed PEEP. Mean driving pressure was 5.6 ± 1 cmH\textsubscript{2}O and 7.4 ± 1 cmH\textsubscript{2}O for the individualized PEEP group and fixed PEEP group, respectively (P < 0.001). The average PEEP was 8 cmH\textsubscript{2}O with a range from 6 to 14 cmH\textsubscript{2}O in the individualized PEEP group [30].

Pereira et al. [32] used electrical impedance tomography to determine individual PEEP such that both lung collapse and hyperdistension are minimized simultaneously in abdominal surgery (n = 40). This study showed PEEP titration reduces driving pressure compared to fixed PEEP 4 cmH\textsubscript{2}O (8.0 ± 1.7 vs. 11.6 ± 3.8 cmH\textsubscript{2}O; P < 0.001). The median PEEP was 12 cmH\textsubscript{2}O but the range varied from 6 to 16 cmH\textsubscript{2}O in the individualized PEEP group [32]. The primary outcome was the size of atelectasis detected in the lung CT taken just after operation. Compared with PEEP 4 cmH\textsubscript{2}O, individualized PEEP patients showed less postoperative atelectasis (6.2 ± 4.1% vs. 10.8 ± 7.1% of lung tissue mass; P = 0.017). Interestingly, this beneficial effects of individualized PEEP for the reduction of driving pressure and atelectasis were more prominent in laparoscopy compared to open surgery [32].

In Park et al. [21], conventional protective ventilation was compared with driving pressure-guided ventilation in thoracic surgery (n = 312). In the driving pressure-guided ventilation, PEEP was titrated to deliver the lowest driving pressure in each patient and applied during one lung ventilation. The PEEP of control group was fixed at 5 cmH\textsubscript{2}O. The incidence of postoperative pulmonary complications measured by Melbourne scale was 12.2% with con-
ventional protective ventilation, and 5.5% with driving pressure-guided ventilation (OR 0.42, P = 0.047) [21]. The mean difference of driving pressure was just 1 cmH₂O [median (IQR), 10 (9 to 11) vs. 9 (8 to 10), P < 0.001] as shown in the previous study of ARDS patients [24]. The authors suggested that the application of individualized PEEP and lower number of patients who showed high driving pressure (> 15 cmH₂O, 1/145 vs. 9/147 patients) as the reasons of better outcomes in driving pressure-guided ventilation group.

According to these few prospective studies, PEEP titration can reduce driving pressure and has a possibility as a more advanced ventilation technique.

**Vₜ titration**

Usually, reduction of Vₜ would decrease driving pressure, but only until the point where reduction of Vₜ does not bring alveolar collapse. In some instances, increased Vₜ was associated with reduction of driving pressure and pulmonary complications [12]. This would probably result from reduction of atelectasis, especially when the level of PEEP is inappropriate [12].

According to 3D lung CT scans, lung size calculation based on the patient's PBW showed discordance with actual lung size frequently. The correlation between actual lung capacity and PBW based on patient's height was not strong (R = 0.58–0.65), and was especially poor in patients with low lung compliance (Fig. 4) [37]. If PBW does not reflect patients’ actual lung size reliably, and patients have different ‘functional lung size’ due to underlying lung pathologies, applying fixed Vₜ based on PBW would frequently result in alveolar over-distension or atelectasis. Therefore, additional Vₜ titration guided by driving pressure may be beneficial. However, no randomized studies are available currently.

**Alveolar recruitment**

Alveolar recruitment is frequently employed to open up the collapsed alveoli before initiation of mechanical ventilation because high PEEP alone is not enough [33,34,38]; When the PEEP increased from 9 to 16 cmH₂O, only 47% of patients showed recruitment, but 53% of patients did not. Oxygenation did not improve and static lung elasticity significantly increased in these patients [39]. Recruitment is also essential before starting PEEP titration for driving pressure measurement. However, we do not know how to recruit lungs with various functional sizes.

These days, the ‘open lung’ approach is gaining popularity as a recruitment technique. The open lung approach is to achieve high levels of lung aeration by first conducting recruitment maneuvers to reverse atelectasis and then applying high levels of PEEP to keep recruited alveoli open [40–46]. Recent open lung approaches use a stepwise increase in inspiratory pressure or Vₜ for the recruitment (inspiratory pressure up to 35–60 cmH₂O, driving pressure up to 20 cmH₂O, or Vₜ up to the ventilator limit), and then

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**Fig. 4.** Computed tomography 3D reconstruction of the lungs. Lung capacity is not well correlated with predicted body weight (PBW). Adapted from Hofman et al. [37].

<table>
<thead>
<tr>
<th>Total lung capacity 1,800 ml</th>
<th>Total lung capacity 3,700 ml</th>
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<tr>
<td>PBW 70 kg</td>
<td>PBW 63 kg</td>
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https://doi.org/10.4097/kja.20041
decremental PEEP titration is performed using volume-controlled ventilation until the highest Cstat is found. The chosen PEEP is usually applied after secondary recruitment (Fig. 5) [40,42,44,45].

However, the open lung approach is not showing consistent results in ICU and surgery. When the open lung approach (recruitment: inspiratory pressure 45 cmH₂O + PEEP 30 cmH₂O, maintenance PEEP: 13 cmH₂O) was compared with a control group (recruitment: inspiratory pressure 20 cmH₂O, maintenance PEEP: 8 cmH₂O) for ICU patients who showed respiratory insufficiency after open heart surgery, pulmonary severity score was lower (score 2.1 vs. 1.8, P = 0.003, OR 1.86), hospital stay (12 vs. 11 days, P = 0.04) and ICU stays (5 vs. 4 days, P = 0.01) were shorter in open lung approach with no difference in in-hospital mortality (n = 320) [47]. Other large scale randomized studies conducted for ARDS patients showed no improvement in clinical outcomes with the open lung approach compared to regular ARDSnet protocol (n = 200, n = 983) [41,48]. Only lung compliance was increased [41] and the incidence of hypoxia was reduced with open lung approach [41,48]. The latest and largest randomized trial called ART showed worse outcomes with the open lung approach compared to an ordinary ARDSnet protocol (n = 1,200) [42]. In this study, the open lung approach was associated with a higher 28-day mortality, 6-month mortality, and fewer ventilator-free days. This poor outcome seems to be related to barotrauma and hemodynamic instability induced by the open lung approach [42].

Besides the above-mentioned ARDS patients, several studies have been published for surgical patients. For abdominal surgery (PROVHILO trial, n = 900), an open lung approach group (recruitment: inspiratory pressure 35 cmH₂O, maintenance PEEP: 13 cmH₂O) was compared to a low PEEP group (≤ 2 cmH₂O) without recruitment [49]. In the open lung approach group, lung compliance improved, but the incidence of hypotension and the use of vasopressors were higher. Postoperative pulmonary complications, the primary outcome, were reported in 40% and 39% in the open lung approach group and low PEEP group, respectively (relative risk 1.01; 95% CI 0.86–1.20, P = 0.86) [49].

For obese patients (PROBESE trial, n = 2,013, BMI ≥ 35), the open lung approach with high PEEP (recruitment: Pplat 40–50 cmH₂O, maintenance PEEP: 12 cmH₂O) was compared to low PEEP (4 cmH₂O) without recruitment in non-cardiac, non-neurological surgery under general anesthesia. Fewer patients showed

![Fig. 5. Representative method of the open lung approach. High pressure stepwise recruitment and decremental PEEP titration is performed. Pplat: plateau pressure, PEEP: positive end-expiratory pressure, TV: tidal volume, VC: volume controlled, PC: pressure controlled, Cstat: static lung compliance, Pr: pressure.](https://doi.org/10.4097/kja.20041)
hypoxemia (SpO$_2$ < 92%) with the open lung approach [5.0% vs. 13.6%, risk reduction −8.6% (95% CI, −11.1% to 6.1%); P < 0.001], but pulmonary complications were not different [21.3% in the high PEEP group, 23.6% in the low PEEP group; risk ratio, 0.93 (95% CI, 0.83 to 1.04); P = 0.23] 

For thoracic surgery, the open lung approach was performed before and after one lung ventilation with the inspiratory pressure 40 and PEEP 20 cmH$_2$O for recruitment. The maintenance PEEP was 8 cmH$_2$O in both the open lung approach and the control groups. The primary outcome was only dead space and PaO$_2$, which were improved with the open lung approach (n = 40) [50].

Overall, the open lung approach seems to improve oxygenation but the beneficial effect on clinical outcome is not certain. Barotrauma may be the main harm of the open lung approach. Barotrauma is an important risk in thoracic surgery and use of recruitment maneuvering at high pressures can cause tension pneumothorax especially in thoracic surgery [51–53].

Opening pressures of normal and collapsed alveoli are known as 0 cmH$_2$O, respectively, and consolidated alveoli never open with even higher pressures (Fig. 6) [38]. Non-recruited portion was almost 24% with open lung approach according to the whole-lung CT in ARDS [54]. Healthy alveoli may be damaged during forceful recruitment of collapsed/consolidated alveoli [25]. In an animal study, large V$_T$ ventilation recruited more alveoli than small V$_T$ ventilation during one lung ventilation, but produced more atelectatic alveoli after the finish of one lung ventilation [55]. Patients who showed a higher percentage of lung recruitment with open lung approach had poorer oxygenation and respiratory-system compliance, and higher rates of death than patients who showed a lower percentage of lung recruitment in ARDS [54]. This may indicate that effective recruitment with the open lung approach only reflects an underlying poor lung condition, but does not necessarily result in improved outcomes.

We do not aim for high oxygenation during ventilation. Instead, we aim for lung protection with acceptable oxygen delivery to tissues. We do not aim for reopening of collapsed/consolidated alveoli at the cost of healthy alveoli. It may be more protective to allow part of the lung to stay closed with permissive atelectasis than to use aggressive effort to keep the lung open [56].

Therefore, regarding recruitment before PEEP titration, we still do not know the best technique for patients with various functional lung sizes. Moderate alveolar recruitment limiting inspiratory pressure < 30 cmH$_2$O or even no recruitment may provide more benefit than the open lung approach [42], but no relevant studies are published yet.

**Application of driving pressure-guided ventilation**

For driving pressure-guided ventilation, we (the Samsung medical center) usually performs recruitment and PEEP titration as follows. First, recruitment is performed by increasing PEEP from 5 up to 15 cmH$_2$O by 5 cmH$_2$O intervals. Each PEEP level is maintained for 4–5 respiratory cycles (requires < 90 s). During recruitment, respiratory rate is 10 /min, inspiratory:expiratory duration = 1:1, inspiratory pause 30%, V$_T$ 8 ml/kg PBW for two lung ventilation, 5 ml/kg PBW for one lung ventilation. Recruitment is stopped if Pplat reaches 30 cmH$_2$O. The second step is
PEEP titration. PEEP starts at 10 cmH\(_2\)O and is then decreased to 0 cmH\(_2\)O by 1–2 cmH\(_2\)O intervals. Driving pressure is measured at each PEEP level after maintaining for 5 respiratory cycles. The PEEP which shows the lowest driving pressure is determined. If multiple levels of PEEP show the same lowest driving pressure, the lowest PEEP is chosen. During PEEP titration, respiratory rate is 12 /min, inspiratory:expiratory duration = 1:2, inspiratory pause 30%, \(V_T\) 8 ml/kg PBW for two lung ventilation, 5 ml/kg PBW for one lung ventilation (requires < 150–275 s). The chosen PEEP is applied throughout the ventilation. Additional recruitment and PEEP titration is performed when driving pressure increases by 2 cmH\(_2\)O from the baseline, or when the ventilator setting is changed. The optional step is \(V_T\) titration. If driving pressure is still higher than 15 cmH\(_2\)O, \(V_T\) is decreased by 1 ml/kg PBW until driving pressure falls below 15 cmH\(_2\)O (\(V_T\) down to 6 ml/kg PBW for two lung ventilation and to 3 ml/kg PBW for one lung ventilation). If driving pressure increases with \(V_T\) reduction, \(V_T\) is increased by 1 ml/kg PBW until driving pressure falls below 15 cmH\(_2\)O (\(V_T\) up to 10 ml/kg PBW for two lung ventilation and to 7 ml/kg PBW for one lung ventilation). Usually, recruitment and PEEP titration finish within 5 minutes and \(V_T\) titration is not required. If driving pressure is maintained higher than 15 cmH\(_2\)O with either method, we expect high postoperative pulmonary complications and prepare more advanced postoperative care.

Currently undergoing large randomized studies for thoracic surgery

PROTHOR

In this study, an open lung approach with maintenance PEEP 10 cmH\(_2\)O is being compared to PEEP 5 cmH\(_2\)O without recruitment (n = 2,378) [43].

iPROVE-OLV

In this study, PEEP 5 cmH\(_2\)O without recruitment is compared to the open lung approach with individualized PEEP based on Cstat (n = 1,380) [44]. The same group used the same protocol for abdominal surgery but failed to show a difference between the two ventilation techniques (iPROVE trial, n = 1,012, relative risk 0.74 to 1.07) [45]. In the previous abdominal surgery study, they performed 4 group comparisons, resulting in an underpowered study. They changed their protocol to a comparison of two groups for the iPROVE-OLV trial [44]. In this trial, individualized high flow O\(_2\) or fixed O\(_2\) supply at post-anesthesia care unit is also included in the protocol.

These studies using individualized PEEP based on Cstat are currently underway. It would be a very important finding if this ventilatory strategy proves to be effective and brings improved outcomes. However, there is a concern regarding the use of a high-pressure open lung approach.

 Conclusion

Driving pressure guided ventilation might be another technique to reduce postoperative pulmonary complications and improve recovery in thoracic and general surgery patients. However, there are not many studies on this topic yet. Thus, more prospective, randomized trials are requested to assess the independent role of driving pressure and PEEP titration for clinical outcomes. \(V_T\) titration based on driving pressure would also warrant further study.

Conflicts of Interest

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

Author Contributions

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Introducing big data analysis using data from National Health Insurance Service

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Among the different providers of health care big data in Korea, the data provided by the National Health Insurance Database include the medical information of all the citizens who have subscribed to medical insurance. As such, the data have representativeness and completeness. In order to conduct research using these National Health Insurance Database data, it is necessary to understand the characteristics of the claim data to avoid various biases, and to control confounding variables when making various operational definitions in the planning stage of the research. Moreover, without a proper understanding of the big data, it is possible during the analysis and data interpretation to mistakenly interpret the correlation between variables as a causal relationship. Therefore, in order to help advanced medical science, which reflects the medical reality such as medical expenses and number of hospital visits by clearly recognizing and analyzing the characteristics and limitations of health care big data, this author has dealt with the use of data sharing services provided by the National Health Insurance Database.

Keywords: Cohort; Correlation; Customized research database; Database; Korea; National Health Insurance; Operational definition; Public health service; Sample research database; Statement.

Research background and purpose

The digitization of documents has led to an abundance in the health care data, which range from electronic medical records used by hospitals to the data collected at the national level. The International Genome Sample Resource, world’s largest human genome variation data released for free on the Amazon web (www.internationalgenome.org), is an example of how to build and use a health care database. The Ontario Institute of Technology, Canada also developed a system to predict pathogen infection by analyzing data from premature infants placed in incubators [1]. The Cleveland Clinic in the United States uses the data collected through its own network to meet the needs of emergency patients.

The Korea National Health and Nutrition Examination Survey, Health Insurance Review and Assessment Service, and National Health Insurance Database are the representatives of health care big data in Korea. Recently, data from four organizations (Korea Center for Disease Control, Health Insurance Review and Assessment Service, National Health Insurance Database, and National Cancer Center) were linked for use in the big data platform for health care (https://hcdl.mohw.go.kr/), providing researchers open access to data for public research purposes. The government is currently devising policies to provide open data for health care research. Through this paper, the author intends to help access this data by understanding the concept of health care big data.
Types and characteristics of health care big data

The data collected through the Korea National Health and Nutrition Examination Survey are different from the data provided by the Health Insurance Review and Assessment Service or the National Health Insurance Database, and are hence suitable for cross-sectional studies with clinical information and blood tests on samples taken from population groups. The Korea Centers for Disease Control and Prevention (https://knhanes.cdc.go.kr/knhanes/main.do) provides open access to data, which can be analyzed with the SPSS statistical packages (SPSS Inc., USA) commonly used by the researchers. On the other hand, the data collected by the National Health Insurance Database and Health Insurance Review and Assessment Service are used for billing medical expenses. Korean nationals are obliged to subscribe for health insurance and pay health insurance premiums as per the insurance subscriber category they belong to. When someone uses medical services, Health Insurance Review and Assessment Service evaluates the medical care expenses incurred by the medical care institution and notifies the industrial complex and that medical care institution of the evaluation results. Since the National Health Insurance Database pays medical care costs to nursing homes based on the information provided by the Health Insurance Review and Assessment Service, it can be considered that the data provided by the National Health Insurance Database and the Health Insurance Review and Assessment Service are almost the same. Data from the Health Insurance Review and Assessment Service can be accessed through the Health Insurance Big Data Open System (http://opendata.hira.or.kr/home.do). The data are paid and are preferably analyzed using statistics processing program such as SAS (SAS institute Inc., USA). Although, compared to the National Health Insurance Database, the data provided by Health Insurance Review and Assessment Service include additional information related to drugs, the sample data have limitations in cohort research. Moreover, it is difficult to access clinical information as there are no screening data.

Among the health care big data providers introduced so far, the author would like to take a deeper look at the data sharing service provided by the National Health Insurance Database. Various studies have been conducted using data from the National Health Insurance Database, such as studies that analyzed socio-economic costs of specific diseases [2–4], studies that described prevalence, mortality, or causes of death [5–8], and studies that analyzed the causes of death according to socio-economic level and disease using the 10th percentile variable of health insurance premium income [9]. Other studies have analyzed mortality or morbidity according to specific medical practices (general anesthesia vs. regional anesthesia) [10,11].

Classification of National Health Insurance Database data

The data collected by the National Health Insurance Database, include detailed treatment practices and prescriptions based on the fee-for-service payment model, and the medical information of all the citizens who have signed up for medical insurance in Korea. Data include insurance eligibility and premiums from birth to death of all citizens, medical history of hospitals and national health examination results, rare refractory and cancer registration information, medical benefits data, and elderly long-term care data since 2002. As the data are provided in the form of a cohort, longitudinal studies are possible, and if a customized database (explained later) is used, studies including those on rare diseases with low prevalence are also possible. In addition, the data on cause and date of death are provided by Statistics Korea (http://kostat.go.kr). The National Health Insurance Database data related to the number of hospitalization days or medical expenses can be used by researchers for cost-effective analysis. Moreover, there is no need to collect or build data separately, and if clinical data are needed, research can be conducted using a screening cohort that actually includes clinical data.

The National Health Insurance Database’s data sharing service is largely divided into customized and sample database (DB). The customized DB is representative of the transmission data provided by de-identifying health insurance and long-term care insurance data collected by the DB. As mentioned earlier, if the researcher aims to study rare diseases, customized DB is recommended because large volume of data can be accessed using the customized DB than the sample DB.

However, to protect patient information, data analysis is to be conducted in a secured room situated in the industrial complex. The sample DB extracts high-demand data as a sample and de-identifies it for analysis, providing a sample cohort DB, medical check-up DB, elderly cohort DB, infant medical check-up DB, and working woman cohort DB. The sample cohort DB, medical check-up DB, and elderly cohort DB include data for 14 years from 2002 to 2015. Of these, the sample cohort DB includes data on 1,025,000 subjects, which is 2% of the total population, and provides data on samples representing the whole nation. The Infant medical check-up DB provides 8 years of data from 2008 to 2015 on 84,000 subjects, as a 5% population of infants who have undergone the 1st to 2nd checkups of infants and toddlers at the 1st and 2nd stages of births between 2008 and 2012 (5 years).
which was simple randomized. However, since the date of birth of the subject is not included, it is difficult to know the exact age of the child. The working women cohort DB includes data of 185,000 subjects, collected for 9 years from 2007 to 2015. Till end of December 2007, 5% of female job enrollers aged 15–64 were randomly extracted.

Both customized and sample DB include an eligibility table showing the health insurance subscriber's eligibility, a death table showing the years of birth and death, a table of injuries showing injuries, number of days spent hospitalized, and total medical expenses, and a table of medical history showing hospital activity and amount\(^1\). In addition, they provide information details of issuance of prescriptions for outpatient use, as well as a sickness history table, which includes all the history of diagnosis received. Furthermore, medical health check-up tables are provided for 54 variables, including smoking, drinking, physical activity, physical measurement, and blood tests. However, information in form of images such as CT scan or ultrasound is not provided. The data for each table are summarized in Table 1.

### Characteristics of National Health Insurance Database data and how to use it

In order to conduct research using National Health Insurance Database data, it is necessary to understand the various characteristics of the claim data. First, it is difficult to know the details of non-salary items (plastic for cosmetic purposes, preventive care, etc.) because both the National Health Insurance Database and the Health Insurance Review and Assessment Service collect data for billing purposes, rather than for research purposes, and include only the salary details in the bill prescribed by the medical institution. Second, it is difficult to grasp the detailed medical history because the cost of a surgery is fixed which is covered by a diagnosis-related group. Third, when diagnosing a patient at the hospital, the severity of the disease tends to increase to avoid reducing insurance claims. On the contrary, even in case of a severe ailment, the sensitivity of the diagnosis may be lowered because the corresponding code may not be entered when it is not related to the salary.

Therefore, in the planning stage of the research, it is necessary to know how sensitive the diagnostic code of each disease is and how to specify the operational definition. To this end, it is imperative to first understand whether a planned research hypothesis can be identified using the particular data.

### Operational definition

Operational definition refers to the condition that best extracts the data of a patient with a specific disease by maximally utilizing information such as diagnosis code, prescription of examination procedural codes, and drugs, which are alternatively available within big data. The degree to which the established operational definition identifies actual target patients and diseases is an important factor in determining the reliability of the study. In the National Health Insurance Database, 20Table provides general information about the wounded and the clinic, and 40Table provides information about all the diagnosis codes including every major and minor diagnosis. The name of the diagnosis is based on the Korean Standard Classification of Disease (6th Revision, KCD-6), which is a revised form of the International Classification of Disease (10th Revision). The National Health Insurance Database continues to study the validity of diagnostic names us-

### Table 1. Tables Provided by National Health Insurance Database

<table>
<thead>
<tr>
<th>Title of the table</th>
<th>Contents of the table</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualification DB</td>
<td>Gender, age, location, type of subscription, social economic variables of the subject such as income rank, disability, death, etc.</td>
</tr>
<tr>
<td>Statement (20Table)</td>
<td>General information of the subject and the clinic, major diagnosis, minor diagnosis, number of days spent hospitalized, total medical expenses, etc.</td>
</tr>
<tr>
<td>Treatment details (30Table)</td>
<td>In-hospital activity (prescription, surgery, materials, etc.), cost of hospitalization, etc.</td>
</tr>
<tr>
<td>Type of disease (40Table)</td>
<td>Every diagnosis including all major and minor diagnoses (ICD-10 codes)</td>
</tr>
<tr>
<td>Prescription details (60Table)</td>
<td>Outpatient prescription details (drug code, dosage, etc.)</td>
</tr>
<tr>
<td>Medical health check-up DB</td>
<td>Composed of 54 variables including smoking, drinking, physical activity, body measurement, and blood test.</td>
</tr>
<tr>
<td>Clinic DB</td>
<td>Status, facility, equipment, and personnel data of clinics by type, establishment, and location.</td>
</tr>
</tbody>
</table>


\(^1\) Statement refers to 20Table, treatment details to 30Table, type of disease to 40Table and prescription details to 60Table which are provided by year basis, statement unit. Therefore, the researcher need to reform the provided tables to make desired data set.
ing various operational definitions\(^2\). Therefore, it is important to examine the validity of operational definition by referencing previous studies in the planning stage.

If there are no existing studies on the validity of operational definitions, researchers need to make sensitive operational definitions by making the most of information such as diagnosis code, prescription of examination and procedural codes, and drugs. For example, in [6], in order to diagnose Parkinson’s disease, the operational definition of the disease was given as follows:

- The patient should at least once be treated using Parkinson’s disease medications such as Levodopa, dopamine agonists (ropinirole, pramipexole, etc.), entacapone, amantadine, selegiline, rasagiline, anticholinergics (trihexyphenidyl HCl, benztropinemesylate, procyclidine) in the general hospital grade neurology department specified in Article 3 of the Medical Code among patients with GCD (Parkinson’s disease) claim code in KCD-6.
- Among them, Parkinson’s disease and Parkinson’s syndrome (G21. Secondary Parkinson’s disease, drug-induced secondary Parkinson’s disease, vascular Parkinson’s disease, etc.; G22. Parkinson’s disease in other classified diseases; G23. Excludes patients with extrapyramidal symptoms and tremors) are included in the claim code as minor diagnosis or suspicion.
- However, the diagnosis codes of G21, G22, G23, and G25 are deleted from the final diagnosis during the disease period among excluded patients, and only G20 is included in the diagnosis of Parkinson’s disease.

In the above study, operational definition including both the diagnostic code and the use of drugs was specified to diagnose patients with Parkinson’s disease. In studies dealing with diseases, it is recommended to define an operational definition with high sensitivity and specificity in parallel with drug use or treatment as in the above study because the diagnosis code may be overextracted or underextracted. If the rheumatoid disease is defined only by serological test results, the specificity is very high, but the sensitivity is low; however, if a patient who is prescribed disease-modifying anti-rheumatic drugs (DMARDs) is searched, sensitivity and specificity can be higher in this operational definition [12].

Research topics so far have mainly dealt with anesthesia and pain medicine including general and regional anesthesia. Data extracted based on procedural code corresponding to the anesthesia type tends to be more accurate compared to data extracted based on diagnosis code which could be overextracted or underextracted. In addition, the total cost of general or regional anesthesia can be utilized to indirectly calculate the anesthesia time, making it easy to apply in research.

**How to control confounding variables**

When planning a study using confounding variables, external confounding and disturbance factors due to internal variables need to be taken into account in the study plan.

External confounding factors include insurance standards such as medical technology, drug codes, treatment codes, and other standards of salary. For example, if a specific medical procedure can be paid for up to 3 times, the treatment method can be changed regardless of whether or not the patient has improved. In addition, it is necessary to understand the medical use behavior, medical treatment process, and clinical environment of doctors based on the unique characteristics of the disease for diseases that are complex and clinically related to the research hypothesis. For example, if a patient has clinical symptoms, such as cognitive dysfunction after surgery, but the symptoms are temporary and do not meet the patient’s medical purpose, the attending doctor can only treat the symptoms without entering the diagnosis code. In the same context, it is also necessary to collect information on the accuracy of the disease as described above, and to verify how well the established operational definition identifies the actual patient or disease.

The internal confounding factor of a study is a factor that can occur in a retrospective study and refers to the relationship of various variables. For example, when the relationship between thyroid cancer and dementia is analyzed and a positive correlation is obtained, a confounding variable that both thyroid cancer and dementia have is a high incidence rate in women. In order to control confounding variables in such cases, the research subject can be ‘restricted’ to ‘women’ or when selecting a control group, gender matching can be used to control the disturbance factors according to gender. In a study analyzing the relationship between type of anesthesia and mortality rate in elderly who have undergone hip fracture surgery, age may act as a disturbing factor when the average age of a general anesthesia group is higher than that of a regional anesthesia group. In this case, it is possible to control the confounding factors according to the age by stratifying and analyzing the patient’s age in the 60s, 70s, 80s, or higher. Alternatively, internal confounding factors can be controlled through multivariate analysis such as linear regression model, logistic regression model, Poisson, and Cox regression.

When analyzing health insurance data, it is difficult to select an ap-
appropriate control group. The patient’s diagnostic code is used to identify the underlying disease, and the Charlson comorbidity index [13] or Elixhauser comorbidity score [14] is used to match the propensity score. The Charlson comorbidity index and the Elixhauser comorbidity score are based on medical data and are thought to be of great help in further research if a shared disease classification system is established that reflects mortality and fatality in surgical patients.

Analyzing National Health Insurance Database

The data provided by the National Health Insurance Database were simply expressed as shown in Fig. 1. The qualification table provides information such as the patient’s ID, age, gender, and income level. If a patient makes multiple claims, initial date of hospitalization, duration of hospitalization, cost of treatment, contents of treatment, and the name of diagnosis can be provided according to each billing unit. However, since the discharge date is not specified in the data provided, it is necessary to rebuild the bill-based data into hospitalization data. For example, if a long-term inpatient has been hospitalized for three months, the bill may be split into three if the patient is billed every month. In this case, if the initial date of hospitalization on the next bill is the same as the date which was added to the duration of hospitalization with initial date of hospitalization in the prior bill, it can be viewed as one hospitalization episode. Furthermore, even if the patient has been transferred to some other hospital, it can be assumed to be one episode if the initial date of hospitalization and the duration of hospitalization is within 2 days of the initial date of hospitalization on the next bill, because it is considered a re-hospitalization for the same diagnosis. This is called an inpatient episode, and when analyzing it, refer to the commands below to help in practice. We would like to show you how to group the inpatient records for each billing unit by the inpatient episode by using the variable for the initial date and the duration of the hospitalization provided in the qualification table (20Table). Instructions were analyzed using SAS v9.4 (SAS institute Inc., USA).

Looking at the SAS command below, since the discharge date is not provided, the hypothetical discharge date (end_date) is set as the initial date of hospitalization (start_date) + duration of hospitalization (mdcare_dd_cnt). If the hypothetical discharge date (end_date) and the next billing start date (start_date2) are within

```
libname sample ‘D:sample’;

data episode1;
set d20;
run;

Data episode2;
Set episode1;
mdcare_start_date = input(put(mdcare_strt_dt,8.),yymmd8.);
Run;
data episode3;
set episode2;
mdcare_end_dt = mdcare_start_date+mdcare_dd_cnt;
keep rn_indi rn_key mdcare_strt_dt mdcare_dd_cnt mdcare_end_dt mdcare_start_date;
run;

proc sort data = episode3;
by rn_indi mdcare_start_date;

Data episode4;
Set episode3;
By rn_indi;
Format start_date start_date2 end_date end_date2 yymmd8.;
start_date = mdcare_start_date;
```
2 days, the same "c" value is given. Finally, the start date of care (start_date2) + the duration of hospitalization (mdcare_dd_cnt) of the invoice with the last c value for each patient identification number is defined as the actual discharge date (end_date2). For better understanding, the result data before and after applying the last c-values were arranged in an Excel file (Supplementary 1).

**Note of caution during big data analysis and data interpretation**

Correlation defines the relationship between two variables by observing whether a variable increases in the same direction or decreases in the opposite direction when the other variable increases. If the two variables move in the same direction, they are said to be in positive correlation, and if they move in opposite directions, they are in a negative correlation. Correlation only indicates the degree of closeness between the two variables; it does not specify the cause and effect of this closeness. On the other hand, causation or causality defines the cause and effect relationship between two variables. For example, it can be seen that there is both a correlation and a causal relationship between height and weight because weight increases with height. However, as weight increases, height does not increase; hence, there is a correlation between weight and height, but there is no causal relationship. Big data has limitation in that it cannot be used to prove the causal relationship, and interpreting the correlation as a causal relationship can result in a huge error. Therefore, in order to not make such an error, it is necessary to make good operational definitions to avoid various biases, and to properly control disturbance variables.

Fisher proposed using the P value as a tool to see how well the data fit the null hypothesis [15]. However, big data includes a vast number of samples, and the P value can be significant for almost all the variables. Therefore, big data analysis has another limitation in that it is difficult to consider the P value as a correct scale for determining statistical significance. Therefore, when analyzing the results, it is better to disclose the CI and effect size rather than relying only on the P value [16]. The P value can only be interpreted as 'with or without a significant difference', but the effect size actually shows how much the difference is, and unlike the P value, the effect size is not affected by the number of samples [16,17]. Though reliance on the P value alone is still debatable, data in recent times has become vast and complicated. There are many cases where reproducibility is difficult only with the P value, and there is a movement to apply the P value more strictly to 0.005 [18]. Alternatively, the null hypothesis and the alternative hypothesis can be compared and tested using the Bayesian statistical hypothesis test [19].

**Summary**

In Korea, the National Health Insurance Database's data sharing service can provide data from a vast number of cohorts. The collected data are based on insurance claims, and have certain limitations. If the researchers clearly recognize and analyze the characteristics and limitations of these data, it is expected to greatly help medical science through research that reflects the medical realities such as medical expenses and number of hospital visits.

**Conflicts of Interest**

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

**Supplementary Materials**

Supplementary 1. Result data before (sheet1) and after (sheet2) applying the last c-values. RN_INDI refers to personal ID. RN_KEY refers to billing status ID.
References

Effects of adding dexmedetomidine to local infiltration of bupivacaine on postoperative pain in pediatric herniorrhaphy: a randomized clinical trial

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Background: Postoperative pain is a major problem, especially in children, as their tolerance level is lower and several drugs are contraindicated in childhood. This study aimed to compare the effect of dexmedetomidine added to local infiltration of bupivacaine for postoperative pain relief in children undergoing inguinal herniorrhaphy.

Methods: This double-blind, randomized clinical trial included 60 children aged 6–72 months undergoing unilateral herniorrhaphy at selected hospitals in Shiraz, Iran, randomly allocated into two groups, 30 in each group. One group received 1 µg/kg dexmedetomidine plus local infiltration of 0.2 ml/kg bupivacaine 0.5% at the incision site before surgery (BD), and the other group received bupivacaine and normal saline (BO). Analgesic requirements, emergence time, and nausea/vomiting, postoperative pain and sedation scores were assessed for 4 h after the operation. Heart rate (HR), systolic blood pressure (SBP), and oxygen saturation (SaO₂) were recorded at baseline, and at 10 and 20 min after injection.

Results: Eighty percent were boy in each group; mean age was 22.75 ± 18.63 months. SaO₂ and SBP were not different between the groups, while HR was significantly lower in the Group BD at 10 and 20 min after injection (P < 0.05). Group BD had a lower pain score at 1 and 2 h after the operation, a higher sedation score at the first three time intervals, and longer emergence time than Group BO (all P < 0.001). Group BD had a lower pain score at 1 and 2 h after the operation (P < 0.001, P < 0.047 respectively).

Conclusions: Addition of dexmedetomidine to local infiltration of bupivacaine in children undergoing herniorrhaphy significantly reduced postoperative pain and increased sedation.

Keywords: Bupivacaine; Child; Dexmedetomidine; Herniorrhaphy; Pain, Postoperative; Vital signs.

Introduction

Indirect inguinal hernia, caused by a patent processus vaginalis, is a common pathology in the first year of life, especially in low-birth weight male neonates [1]. Surgery (inguinal herniorrhaphy) is considered to be the first-line treatment, in which various techniques, such as open and laparoscopic procedures, have been proposed [2]. Nevertheless, despite the variety of techniques proposed for correction of inguinal hernia, herniorrhaphy is associated with severe adverse effects, such as recurrence, and persistent postoperative pain [3,4].
Among the postoperative adverse effects, pain has significant importance, especially in children, because uncontrolled acute pain may lead to chronic pain that can increase patient stress and negatively affect health-related quality of life. It can also increase the duration of hospital stay and total health costs [5]. Thus, researchers have investigated the efficacy of various analgesics, including bupivacaine, levobupivacaine, clonidine and naloxone, on post-herniorrhaphy pain in children administered at different times through various routes [6,7] such as caudal analgesia, inguinal nerve block, or local infiltration combined with a general anesthetic [8]. However, review studies have reported no significant differences among the various strategies [9].

Dexmedetomidine (DEX) is a highly selective α₂-adrenergic agonist with a receptor affinity greater than clonidine, which acts through various mechanisms, such as increased hyperpolarization of action potential, causing hypnotic and analgesic effects [10]. Adding DEX as an adjuvant to bupivacaine has proven effectiveness for postoperative pain relief in various procedures such as cesarean section [11], abdominal hysterectomy [12], and knee arthroplasty [13]. Even a combination of DEX with bupivacaine has been proposed to be superior to bupivacaine alone or with tramadol in cholecystectomy procedures [14]. In children undergoing lower abdominal procedures, adding DEX to caudal bupivacaine increased analgesia without side-effects [15,16]. Recently, researchers reported the extended duration of postoperative pain relief and reduced response to hernial sac traction using 1 μg/kg DEX combined with bupivacaine in children undergoing hernia repair [17,18]. Higher doses of DEX has also been proposed as a feasible anesthetic in pediatric inguinal hernia repair [19]. Furthermore, premedication with sublingual DEX has been established to be more effective than sublingual midazolam in children < 12 years of age undergoing inguinal hernia repair [20].

Local infiltration of drugs into surgical wounds is considered to be an effective measure in reducing postoperative pain and a safe method because it does not exert the hemodynamic effects of the drug when administered intravenously [21]. A combination of DEX with a local anesthetic, such as bupivacaine or ropivacaine, has been suggested as an appropriate method for postoperative pain relief in adult patients undergoing abdominal hysterectomy [22] and lower segment cesarean section [23]. However, to our knowledge, the effect of combining DEX with bupivacaine has not been described in the pediatric population. Thus, in the present study, we aimed to assess the combined effect of DEX and local infiltration of bupivacaine to improve postoperative pain relief in children undergoing inguinal herniorrhaphy.

Materials and Methods

Study design

This randomized clinical trial involved 60 children undergoing unilateral herniorrhaphy in Nemazee and Ghadir Hospitals, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. The study protocol was approved by the Research Ethics Committee of Shiraz University of Medical Sciences (Approval number: IR.SUMS.REC.1394.5.945) and was registered in the Iranian Registry of Clinical Trials (IRCT2016060314372N8). Before participant recruitment, the objectives of the study were explained to the parents of the children and written informed consent was obtained. The study adhered to the principles outlined in the Declaration of Helsinki.

Based on the calculated sample size, 60 children 6–72 months of age with unilateral inguinal hernia and American Society of Anesthesiologists (ASA) class I were included in the study. Children with developmental problems, intellectual disabilities, history of seizures, coagulopathies, sensitivity to DEX and bupivacaine, congenital heart disease, history of bleeding disorders, upper respiratory tract infection, liver or kidney failure, and neurological diseases were excluded from the study. A flow diagram illustrating patient recruitment is shown in Fig. 1.

Fig. 1. Flow diagram illustrating study enrollment. CHIPPS: Children and Infants Postoperative Pain Scale.

https://doi.org/10.4097/kja.19111
The included patients were randomly divided into two groups based on a computer-generated list: one group received 1 µg/kg DEX (Precedex, Pfizer Inc., USA) plus local infiltration of 0.2 ml/kg bupivacaine 0.5% (Group BD); and the other group received local infiltration of 0.2 ml/kg bupivacaine 0.5% with 1 ml normal saline (Group BO), which were prepared before surgery in similar syringes. The prepared drugs were injected at the surgical site immediately before incision.

The patients were kept in a “nothing by mouth” state the night before surgery but could drink liquids up to 3 h before the procedure. Approximately 20 to 30 min before entering the operating theater, all patients received 0.5 mg/kg oral midazolam for sedation. After entering the operating theater, intravenous (IV) cannulation with a size 22–24 cannula was performed. Then, patients were infused with 6 ml/kg IV fluid (1/3 normal saline, 2/3 dextrose water). Anesthesia was induced by an anesthesiologist using 7 mg/kg sodium thiopental and continued with 2–3% sevoflurane, oxygen, and nitrous oxide through a facial mask. Vital signs, including heart rate (HR), blood pressure (BP), and oxygen saturation (SaO₂) were recorded at three time points: baseline, and 10 and 20 min after injecting the study drugs. All procedures were performed by a surgical team using a similar method.

The drugs were prepared before surgery in similar syringes and provided to the surgeon, who was blinded to the group allocation. The drugs used in this study were prepared by an investigator who was not involved in the other parts of the study. The anesthesiologist, surgeon, and nurses were not aware of the content of the syringes. Monitoring during surgery included electrocardiography, pulse oximetry, and non-invasive blood pressure measurement. At the conclusion of the procedure, the patients were transferred to the post-anesthesia care unit, where their vital signs were monitored every 15 min by a nurse.

The sedation level and severity of pain (based on the Children’s and Infant’s Postoperative Pain Scale [CHIPPS]) were assessed by an expert nurse at 1, 2, 3, and 4 h after surgery. In cases for which CHIPPS score was ≥ 3, 15 mg/kg acetaminophen (Apetel, Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A., Greece) was infused and, in cases of nausea/vomiting, 0.15 mg/kg ondansetron was administered. Additionally, analgesic requirements, time of emergence, and nausea/vomiting were recorded for all participants by the same nurse. Sedation score was calculated as follows: 0 = patient is awake and alert; 1 = mild sedation, easy to rouse; 2 = asleep, easy to rouse; 3 = moderate sedation, inability to remain awake; and 4 = difficult to rouse [18]. Emergence time was defined as the time from the conclusion of surgery until eye opening following calling of the child’s name.

The primary endpoint of this study was postoperative analgesia; secondary endpoints included postoperative sedation, hemodynamic change, and emergence time.

Statistical analysis

The minimum sample size required for this study was calculated to be 23 in each group using the sample size estimation formula to compare mean values considering a confidence level of 95%, a power of 80%, standard deviation (SD) of 0.90 and 0.85, and difference of means between the groups at 0.75 (these figures were gathered from the study by Xiang et al. [18]). To address the possibility of drop out, 30 patients were included in each group, resulting in a total of 60 patients. Data are expressed as mean and SD for parametric, and median with range for non-parametric variables. The independent t-test was used to compare normally distributed variables, and the Mann-Whitney U test for pain and sedation score, emergence time, and duration of surgery between the groups. SPSS version 21.0 (IBM Corp., USA) for Windows (Microsoft Corp., USA) was used for statistical analysis. Differences with P < 0.05 were considered to be statistically significant.

Results

A total of 60 patients were recruited for the study, with 30 patients (24 [80%] boys, 6 [20%] girls) in each group. The mean age of the participants was 22.75 ± 18.63 months (27.97 ± 20.78 months in the Group BD versus 17.53 ± 14.77 months in the Group BO). The age distribution of the participants in the two groups is summarized in Table 1, which shows that the highest frequency was the age category of < 12 months in both groups.

A comparison of vital signs between the groups at the three time points is shown in Table 2. There was no difference between the groups regarding SaO₂ and SBP (P > 0.05), while HR was significantly lower in the Group BD at 10 and 20 min after injection.
There was a significant time effect on HR (P < 0.001), and group × time interaction (P < 0.008). Additionally, time had a significant effect on \(\text{SaO}_2\); however, the trend in changes during time was not different between the groups (P = 0.5). Time did not have a significant effect on SBP (P = 0.08), and there was no difference between the groups in trends in changes in SBP during the study (P = 0.3).

In the Group BD, the median pain score was significantly lower than in the Group BO at 1 h and 2 h after the operation (P < 0.001); however, there was no significant difference in median pain scores between the groups at 3 h and 4 h after the operation (Table 3). The effect of time was statistically significant in both groups (P < 0.001 and P < 0.003, respectively).

The sedation score was significantly higher in the Group BD at the first three time points (1, 2, and 3 h after surgery) (P < 0.001). The effect of time was statistically significant in the Group BD (P < 0.001), but not in the Group BO (P = 0.8) (Table 3).

Emergence time was significantly longer in the Group BD (20 min [range, 10–25 min]), compared with the Group BO (5 min [range, 3–20]) (P < 0.001); duration of surgery was not different between the two groups (P = 1.0). No episode of nausea or vomiting was recorded.

**Discussion**

The results of the present study showed no statistically significant differences in \(\text{SaO}_2\) and SBP between the two groups. HR in the Group BD was significantly lower compared with the Group BO at 10 and 20 min after infiltration of the drugs; however, there was no statistically significant change in HR in each group. Several studies have demonstrated the greater analgesic effect of DEX plus bupivacaine in caudal analgesia compared with bupivacaine alone in children undergoing lower abdominal procedures under sevoflurane anesthesia, without significant side effects, and have

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**Table 2. Comparison of Heart Rate, Oxygen Saturation, and Systolic Blood Pressure at Three Different Time Points**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group BD</th>
<th>Group BO</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>125.2 ± 14.3</td>
<td>133.5 ± 16.8</td>
<td>0.054</td>
</tr>
<tr>
<td>10 min post-injection</td>
<td>122.5 ± 15.3</td>
<td>135.1 ± 15.9</td>
<td>0.004</td>
</tr>
<tr>
<td>20 min post-injection</td>
<td>118.1 ± 13.1</td>
<td>128.3 ± 12.0</td>
<td>0.008</td>
</tr>
<tr>
<td>Oxygen saturation ((\text{SaO}_2)) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>97.1 ± 2.8</td>
<td>97.2 ± 2.6</td>
<td>0.858</td>
</tr>
<tr>
<td>10 min post-injection</td>
<td>99.3 ± 0.6</td>
<td>99.1 ± 0.9</td>
<td>0.388</td>
</tr>
<tr>
<td>20 min post-injection</td>
<td>99.3 ± 0.6</td>
<td>98.8 ± 1.6</td>
<td>0.251</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>99.6 ± 12.8</td>
<td>94.1 ± 13.4</td>
<td>0.120</td>
</tr>
<tr>
<td>10 min post-injection</td>
<td>94.9 ± 10.0</td>
<td>93.5 ± 13.9</td>
<td>0.668</td>
</tr>
<tr>
<td>20 min post-injection</td>
<td>95.9 ± 11.3</td>
<td>92.3 ± 12.3</td>
<td>0.300</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Results of independent t test. Group BD: bupivacaine + dexmedetomidine, Group BO: bupivacaine + normal saline.

**Table 3. Comparison of Pain and Sedation Scores at Different Postoperative Intervals**

<table>
<thead>
<tr>
<th>Pain/sedation</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group BD</td>
<td>0 (0, 3)</td>
<td>0 (0, 3)</td>
<td>0 (0, 1)</td>
<td>0 (0, 0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Group BO</td>
<td>3 (2, 5)</td>
<td>1 (0, 2)</td>
<td>0 (0, 1)</td>
<td>0 (0, 0)</td>
<td>0.003</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>0.047</td>
<td>0.765</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Sedation score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group BD</td>
<td>2 (0, 4)</td>
<td>1 (0, 2)</td>
<td>0 (0, 1)</td>
<td>0 (0, 0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Group BO</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
<td>0 (0, 0)</td>
<td>0 (0, 2)</td>
<td>0.801</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.283</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range). The pain score was assessed according to the Children and Infants Postoperative Pain Scale (CHIPPS). Group BD: bupivacaine + dexmedetomidine, Group BO: bupivacaine + normal saline. *P value for Friedman test. †P value for Mann-Whitney U test.
Azemati et al. · Post-op pain in pediatric herniorrhaphy

proposed similar adjuvant efficacy for DEX and clonidine [15,16]. These results are consistent with those of the present study, indicating the high analgesic and sedative effect of DEX when added to other anesthetics, although the type of anesthetic and administration method was different. In accordance with our study, Saadaway et al. [17] also confirmed significantly longer sedative and analgesic effects in the Group BD than Group BO in 60 children 1–6 years of age with ASA class I undergoing inguinal hernia repair. They concluded similar pain scores in the first 4 h between the BD and BO groups, which is inconsistent with our results, given that we observed lower pain scores in the Group BD 1 h and 2 h after surgery. This difference could be attributed to the different pain scale (objective pain scale) used in their study [17]. Xiang et al. [18] demonstrated that supplementation of 1 µg/kg DEX to caudal bupivacaine could extend the duration of postoperative pain relief and reduce the need for rescue analgesia. This is consistent with the results obtained in the present study, at 1 h postoperatively, 22 patients in the Group BD (73.3%) had a CHIPPS score of 0, while 24 (80%) in the Group BO had a CHIPPS score of 3 (P < 0.001). At 2 h postoperatively, 21 (70%) patients in the Group BD and 11 (36.6%) in the Group BO had CHIPPS scores of 0 (P < 0.006). However, they demonstrated no statistical difference in CHIPPS pain scores between the two groups until 4 h [18]. In their study, during the first 4 h, analgesia was adequate in all subjects of both groups. As the results of the study by Xiang et al. [18] demonstrated, adding DEX to caudal bupivacaine prolonged the duration of postoperative analgesia.

The results of our study investigating the analgesic effect of DEX administered as surgical site infiltration as an adjunct to bupivacaine are consistent with those of previous studies investigating adding DEX to other local anesthetics. Several studies have investigated the effect of adding DEX to ropivacaine, administered as an incisional infiltration, in different procedures, such as inguinal hernia [24], laparoscopic cholecystectomy [25], and lower segment cesarean section [23]. The results of these studies demonstrated significantly lower visual analogue scale (VAS) scores until 24 h after surgery in the DEX + ropivacaine group compared with ropivacaine alone, while nausea/vomiting or other complications were not different between the groups. Although the general results of these studies confirm the efficacy of adding DEX to local anesthetic, there were several differences between them and our study. First, the type of local anesthetic used was different (ropivacaine versus bupivacaine). Second, the study populations were different because they investigated adult populations, while we evaluated pediatric patients. In addition, in the current study, we used CHIPPS for assessment of postoperative pain, similar to the study by Xiang et al. [18], while other studies alternatively used other scales, such as the Face, Legs, Activity, Cry, Consolability Pain Scale [15], the OPS [17], and VAS [23–25]. Nevertheless, they all reported similar conclusions regarding the efficacy of adding DEX to bupivacaine and other local anesthetics in adults and children. Other studies have also indicated the efficacy of incisional infiltration of DEX on postoperative pain relief, supplemented with other anesthetics, such as levobupivacaine [26], lignocaine with adrenaline [27], suggesting that co-infiltration of local anesthetics can prolong their anesthetic and analgesic effect by peripheral action [28].

Another important finding of our study was significant higher sedation scores in the Group BD at the first three time points (i.e., 1, 2, and 3 h after surgery) as well as longer emergence time in this group, which indicate deeper sedation in Group BD, which is similar to the results reported by Xiang et al. [18] and others. In the study by Abdelnaim et al. [29], the researchers reported significantly higher Ramsay sedation scores in the Group BD compared with BO and DEX + magnesium groups, which confirms the results of our study. It has been previously indicated that IV administration and infiltration of DEX results in greater sedation compared with normal saline [30]. The sedative effects of DEX are mainly the result of the stimulation of α₂-adrenoceptors in the locus coeruleus [18]. Evaluation of the postoperative sedation scale in our study reveals more satisfactory sedation in the Group BD compared with the Group BO in the first three hours.

Strengths of the present study include the assessment of adjuvant efficacy of local infiltration of DEX in children undergoing inguinal hernia repair in a double-blind RCT. Nevertheless, the present study had some limitations, the first of which was the age difference between the two groups, despite the random allocation of participants and sufficient sample size, which may have affected the results of the study. Additionally, we evaluated patients for only 4 h after surgery; as such, longer follow-up periods may provide a wider spectrum for the best drug choice for researchers and physicians.

Local infiltration of DEX as supplementation to bupivacaine can significantly reduce postoperative pain in children undergoing herniorrhaphy, especially in the first postoperative hour, and can induce higher sedation after surgery without significant side effects on the hemodynamic status of pediatric patients. Thus, it is suggested that local infiltration of DEX be used as adjuvant therapy with bupivacaine after pediatric herniorrhaphy. Future studies with longer follow-up periods and larger populations may reveal the best anesthetic for children undergoing inguinal hernia repair.
Funding Statement

This study was financially supported by Shiraz University of Medical Sciences (Grants No. 8189).

Conflicts of Interest

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

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Association of trainee involvement in an acute pain service with postoperative opioid use in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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**Background:** Several hospitals have implemented a multidisciplinary Acute Pain Service (APS) to execute surgery-specific opioid sparing analgesic pathways. Implementation of an anesthesia attending-only APS has been associated with decreased postoperative opioid consumption, time to ambulation, and time to solid food intake for patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. In this study, we evaluated the impact of introducing an APS trainee on postoperative opioid consumption in patients undergoing hyperthermic intraperitoneal chemotherapy during postoperative day (POD) 0–3.

**Methods:** We performed a retrospective propensity-matched cohort study where we compared opioid consumption and hospital length of stay among two historical cohorts: attending-only APS versus service involving a regional anesthesia fellow.

**Results:** In the matched cohorts, the median POD 0–3 opioid use [25%, 75% quartile] for the single attending and trainee involvement cohort were 38.5 mg morphine equivalents (MEQ) [14.1 mg, 106.3 mg] and 50.4 mg MEQ [28.4 mg, 91.2 mg], respectively. The median difference was –9.8 mg MEQ (95% CI –30.7 to 16.5 mg; \(P = 0.43\)). There was no difference in hospital length of stay between both cohorts (\(P = 0.67\)).

**Conclusions:** We found that the addition of a regional anesthesia fellow to the APS team was not associated with statistically significant differences in total opioid consumption or hospital length of stay in this surgical population. The addition of trainees to the infrastructure, with vigilant supervision, is not associated with change in outcomes.

**Keywords:** Acute pain service; Epidural; Opioids; Trainee.

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**Introduction**

Inadequate postsurgical pain control has been associated with adverse events including myocardial ischemia, ileus, pulmonary infections, anxiety, thromboembolism, as well as chronic persistent postoperative pain \([1]\). Similarly, patients with persistently poorly controlled pain throughout their admission are more likely to have 30-day readmission or...
subsequent emergency department visits [2]. Reliance on uni-modal opioid therapy for pain management has resulted in serious side effects [3] leading to the evolution of multimodal analgesia as part of the practice guidelines for perioperative pain management [4]. Several hospitals have implemented a multidisciplinary Acute Pain Service (APS) to execute these surgery-specific opioid sparing analgesic pathways.

The implementation of an anesthesia attending-only APS has been associated with decreased postoperative opioid consumption, time to ambulation, and time to solid food intake for patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) [5]. In September 2017, the APS at our institution introduced a regional anesthesia fellow into the APS team. In this propensity-matched cohort study, we evaluated the impact of introducing an APS trainee on postoperative opioid consumption in patients undergoing CRS-HIPEC during postoperative day (POD) 0–3.

Materials and Methods

Data was collected retrospectively from the data warehouse of our institution. All data for surgical patients that were scheduled for a CRS-HIPEC from 2016 to 2018 was extracted. The resulting dataset remained de-identified and did not contain sensitive patient-health information as defined by the institutional Human Research Protections Program, and therefore, was exempt from the informed consent requirement and approved by our University of California, San Diego Institutional Review Board (UCSD IRB no. 190559).

This was a retrospective cohort study in which the primary objective was to determine if there was a decrease in median total opioid consumption (intravenous morphine equivalents [MEQ]) during POD 0–3 among CRS-HIPEC patients whose pain was managed by a single anesthesiology attending provider versus a team consisting of an anesthesiology attending and a trainee (regional anesthesia and acute pain fellow) in the setting of APS. During 2016 to mid-2017, APS consisted of a single anesthesiology attending provider fellowship-trained in either regional anesthesia and acute pain or chronic pain. Thereafter, a weekly rotating trainee (regional anesthesia and acute pain fellow) was introduced into the APS team. The multimodal analgesic regimen implemented by APS includes preoperative pregabalin, scopolamine patch, and pre-operative thoracic epidural placement in addition to around-the-clock dosing of acetaminophen. This protocol has not changed with the addition of trainees to the APS model. We sought to determine if there was an association of trainee involvement in opioid consumption. Fig. 1 illustrates patient inclusion criteria. We performed a propensity-matched (controlling for age, body mass index, sex, and primary cancer site) comparison. Between matched cohorts, we compared median opioid consumption during POD 0–3 using Wilcoxon rank sum test. An absolute standardized mean difference of less than 0.2 between cohorts among each confounder variable was considered adequately matched. The median difference and 95% CI were calculated using the Hodges-Lehman estimator. A P < 0.05 was considered statistically significant. The manuscript adheres to the applicable Equator guidelines.

Results

There were a total of 51 patients managed by a single anesthesiology attending versus 42 patients in the trainee involvement cohort. In the unmatched cohorts, the median POD 0–3 opioid use [25%, 75% quartile] for the single anesthesiology attending versus the trainee involvement cohort were 27.5 mg MEQ [7.6 mg, 106.25 mg] versus 50.4 mg MEQ [28.4 mg, 91.2 mg], respectively, with a median difference of –15.2 mg MEQ (95% CI 33.8–5.40 mg MEQ, P = 0.14). Demographic variables between the propensity-matched cohorts all had a standardized mean difference < 0.2, and therefore were considered appropriately matched (Table 1). In the matched cohorts, the median POD 0–3 opioid use [25%, 75% quartile] for the single anesthesiology attending and trainee involvement cohort were 38.5 mg MEQ [14.1 mg, 106.3 mg] and 50.4 mg
MEQ [28.4 mg, 91.2 mg], respectively. The median difference was –9.8 mg MEQ (95% CI –30.7 to 16.5 mg; P = 0.43). (Fig. 2). There was no difference in hospital length of stay between both cohorts (P = 0.67).

**Discussion**

We found no statistically significant differences in total opioid consumption on POD 0–3 in patients undergoing CRP-HIPEC when the APS team consisted of an anesthesia attending and trainee, compared to a single anesthesiology attending. Likewise, there was no statistically significant difference in hospital length of stay between the two groups. The success of APS in reducing opioid requirement is multifactorial, and includes implementation of multimodal analgesic regimens, patient education, close follow-up, and successful pre-operative placement of thoracic epidural analgesia (TEA). The addition of trainees to the infrastructure, with vigilant supervision, is not associated with change in outcomes. The multimodal analgesic regimen implemented by APS includes preoperative pregabalin, scopolamine patch, and pre-operative thoracic epidural placement in addition to around-the-clock dosing of acetaminophen [5]. This protocol has not changed with the addition of trainees to the APS model. Likewise, every epidural placed in the pre-operative holding area was tested with ice, and a bilateral sensory level to ice confirmed before going to the operating room [5]. Epidural catheters that did not have a bilateral sensory level to ice were removed, thus only patients with epidural catheters that had a positive bilateral sensory level loss to ice were included in this study.

As Tran and Krodel [6] pointed out, logistics about optimal organization of an APS is a question that has yet to be resolved. Infrastructure varies widely between institutions, some incorporating attending residents, and fellows in Anesthesiology only, while others are multidisciplinary integrating pharmacists, psychologists, and physiotherapists into their infrastructure [7]. As Tran and Krodel discusses, there are short-term upsides to single anesthesiology attending only APS, including assurance in block success in terms of neuraxial procedure as well as vigilance in patient follow-up and optimization of established protocols. However, an infrastructure of a one-person service is non-sustainable and does not allow for growth. Likewise, in an academic institution, such infrastructure can limit opportunities for valuable educational experiences in multimodal analgesia, as well as one-on-one expert instruction in TEA placement for trainees.

### Table 1. Demographics between Propensity-matched Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Single anesthesiology attending only acute pain service</th>
<th>Attending and trainee acute pain service</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>42</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>52.1 ± 13.5</td>
<td>51.9 ± 12.9</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 ± 6.2</td>
<td>27.5 ± 5.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>20 (47.5)</td>
<td>20 (47.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Primary cancer site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendiceal</td>
<td>30 (71.4)</td>
<td>28 (66.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>Colon</td>
<td>5 (11.9)</td>
<td>6 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>4 (9.5)</td>
<td>5 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>1 (2.4)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>1 (2.4)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>1 (2.4)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). SMD: standardized mean difference, BMI: body mass index.

![Fig. 2. Total opioid consumption postoperative day 0–3 propensity-matched analysis. Box plot demonstrating difference in opioid consumption during postoperative days 0–3 in the no trainee versus trainee cohort for the acute pain service. IV: intravenous.](https://doi.org/10.4097/kja.19370)
TEA procedure continues to be a challenging procedure for anesthesiologists with failure rates as high as 32% in large teaching institutions [8,9]. Unfortunately, opportunities for trainees to learn TEA seem to be decreasing [10] due to a variety of reasons including falsely perceived increased risk of complications, inexperienced supervisory role, and introduction of alternative blocks such as transverse abdominis plane blocks [8]. At UCSD, it is not surprising that the quality of outcomes has not changed with the addition of trainees given the established setup of APS workflow: 1) early discussion of the analgesia plan with the surgical team, 2) efficient workflow with patient and nursing check-in, 3) supervising the attending specialized in regional anesthesia and highly experienced in TEA placement, and 4) ample time allowed to test block success defined by sensory deficit. Even with trainees involved, such organization allows for such system to be setup for success.

Limitations of this study include its retrospective design, which may involve unmeasured confounders. Likewise, preoperative and intraoperative opioid data was not collected, which could affect postoperative opioid requirement. Although our APS manages a variety of surgical populations, we chose to focus on CRS-HIPECs to maintain consistency in the population and because they tend to use the highest opioids among major surgery. Furthermore, we may be under-powered to detect any real differences. A larger prospective randomized controlled trial will be required to answer this question definitively.

In conclusion, including trainees to APS infrastructure is not associated with change in patient outcomes in terms of postoperative opioid requirement or hospital length of stay.

Conflicts of Interest

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

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Whole-blood hypocoagulable profile correlates with a greater risk of death within 28 days in patients with severe sepsis

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Background: Hypocoagulability and impaired platelet function have been associated with a high risk of death in sepsis. The aim of this cohort study was to determine whether sepsis-induced hypocoagulability and platelet dysfunction (assessed by ROTEM® and MULTIPLATE®, respectively) are increased in sepsis patients who died within 28 days after diagnosis compared with patients who died between 29 and 90 days after diagnosis.

Methods: Consecutive patients admitted to the intensive care unit of Padova University Hospital from March 2015 to March 2018 for severe sepsis were considered. We collected blood samples from all patients to determine ROTEM® and MULTIPLATE® parameters. Each enrolled patient underwent a 90-day follow-up and the mortality rate was recorded.

Results: Of 120 patients, 36 (30%) died within 28 days post-diagnosis (Group A), 23 (19%) died between days 29 and 90 post-diagnosis (Group B), and 61 (51%) were alive after 90 days (survivors). The clotting time in the ROTEM® test and clot formation time in the EXTEM test were significantly more prolonged in Group A than in B. Both groups showed a significantly higher hypocoagulability than survivors in the EXTEM test. MULTIPLATE® platelet function analysis showed that platelet function was significantly lower in Group A than in Group B.

Conclusions: The present study showed that the combination of thromboelastometry and impedance aggregometry may help identifying sepsis patients at high risk of short-term death. Larger studies are warranted to corroborate our results.

Keywords: Coagulopathy; Hypocoagulability; MULTIPLATE; ROTEM; Severe sepsis; Thrombelastography.

Introduction

Despite continually updated sepsis/septic shock guidelines and bundles [1] recommending early diagnosis and prompt initiation of therapy, sepsis remains a challenge worldwide. The overall mortality rate of septic shock ranges from 25–30%, reaching 40–60% among hospitalized patients [1–5]. Sepsis is a complex systemic defense mechanism to an overwhelming infection. The inflammatory response against an invading pathogen is the result of several hemostatic alterations, notably the dysregulation of pro- and anti-coagulant factors [6–9]. Although hypocoagulability appears to accurately predict a fatal outcome in sepsis, conventional coagulation tests are unable to reliably detect sep-
sis-induced coagulopathy [10]. In addition, recent reports have shown that platelet function and inflammation are tightly linked [10,11]. Platelets may act as circulating sentinels, binding to infectious agents and presenting them to the reticuloendothelial system [11]. However, experimental findings on platelet aggregation in response to bacteria have yielded conflicting results [11]. Thus, we aimed to evaluate whole-blood coagulation and platelet function in a cohort of patients with severe sepsis via whole-blood thromboelastometry by ROTEM® (Tem International GmbH, Germany) and impedance aggregometry by MULTIPLATE® (Roche Diagnostics GmbH, Germany).

Materials and Methods

All consecutive patients admitted to the intensive care unit (ICU) of Padova University Hospital between March 2015 and March 2018 with a diagnosis of severe sepsis — according to the Surviving Sepsis Campaign criteria [12] — were considered for enrollment. The diagnosis of severe sepsis was established within 6 hours of ICU admission and each septic patient admitted to our ICU was managed according to Sepsis 2 guidelines (before 2016) and Sepsis 3 guidelines (after 2016) [12]. Exclusion criteria were: Younger than 18 or older than 90 years of age, ongoing pregnancy, Child’s C liver disease, New York Heart Association (NYHA) class IV heart disease, chronic kidney disease, metastatic cancer, pre-existing hematological disorders, readmission to ICU, septic shock, ongoing antiplatelet or anticoagulant therapy, and reception of platelets, fresh frozen plasma or other coagulant substances during the 24 hours preceding the enrollment.

All patients were enrolled within six hours after ICU admission. At time of enrollment, i) informed consent was obtained from each patient or their relatives; ii) demographic and clinical data regarding source of infection, comorbidities (e.g., cancer, diabetes) were collected; iii) Sequential Organ Failure Assessment (SOFA) and Japanese Association for Acute Medicine (JAMA) scores were calculated [13,14]; and iv) two BD vacutainers (Becton Dickinson, USA) with sodium citrate 109 mmol/L (3.8% sodium citrate) and one vacutainer with ethylene-diamine-tetra acetic acid 5.4 mg were collected.

All patients (when available) or their relatives received a monthly follow-up telephone call to ascertain the vital status of patients for up to 90 days after the diagnosis of severe sepsis. Thereafter each patient was placed in one of the following groups: Patients in Group A deceased within 28 days post-diagnosis and patients in Group B deceased between days 29 and 90 post-diagnosis. The patients still living 90 days post-diagnosis were labeled ‘Survivors.’

The protocol was approved by the Institutional Ethical Committee on March 19, 2015 (Ref: 3419/AO/15). The study was performed in compliance with the Declaration of Helsinki and in accordance with the STROBE statement (Supplementary Table 1).

The cohort of patients reported in the present study has been partially described in previous studies [15,16].

Laboratory tests

Blood cell counts, coagulation and chemistry parameters were measured using standardized laboratory methods. Thromboelastometry and platelet function tests were performed within three hours of blood collection on citrated whole blood by trained personnel using an automated ROTEM® delta device (Tem International GmbH, Germany) and a MULTIPLATE® function analyzer (Roche Diagnostics GmbH, Germany) [17] according to standardized procedures and the manufacturer’s recommendations. EXTEM, INTEM, and FIBTEM assays were performed for each enrolled patient and the following parameters were measured: i) clotting time (CT, s), the time from the beginning of the coagulation analysis until an increase in amplitude of 2 mm. CT reflects the activation phase of whole-blood clot formation; ii) clot formation time (CFT, s), the time elapsed for an increase in amplitude of the thromboelastogram from 2 to 20 mm. CFT reflects the propagation phase of whole-blood clot formation; iii) maximum clot firmness (MCF, mm), the maximum amplitude reached in the thromboelastogram; iv) thrombodynamic index (TDI), MCF/CT + CFT to globally assess a patient’s whole-blood coagulation capabilities [16].

The MULTIPLATE® platelet function analysis takes place in a single-use test cell, which incorporates dual copper sensor wires [17]. When activated, platelets adhere to the sensor wires thus increasing the electrical resistance (i.e., impedance). This increase is proportional to the capability of platelets to aggregate on each wire. The results are expressed as Area Under the Curve (AUC, AU*min). The greater the area the more platelets aggregate. Platelets were stimulated in three different ways: i) using adenosine diphosphate (ADP) to activate the ADP receptor (ADP test, Roche Diagnostics GmbH, Germany); ii) via arachidonic acid, checking cyclooxygenase-dependent aggregation (ASPI test, Roche Diagnostics GmbH, Germany); iii) using thrombin receptor-activating peptide-6 (TRAP-6) to activate the thrombin receptor (TRAP test, Roche Diagnostics GmbH, Germany).

Statistical analysis

The sample size calculation was based on previous observations
and the following assumptions: i) expected difference in TDI EXTEM between survivors and non-survivors of 0.06 ii) expected standard deviation (SD) of 0.01; iii) power = 90%; and iv) alpha = 0.05. Based on these assumptions, we needed two groups (e.g., survivors and non-survivors) of at least 55 patients each. Categorical variables were described as frequencies, and comparisons were performed with Fisher's exact test. The normality assumption was assessed with the Shapiro-Wilk normality test. The ANOVA test and the Bonferroni post-hoc analysis were performed for parametric variables. The Kruskal-Wallis test and Dunn's multiple comparisons post-hoc analysis were used for non-parametric variables. In addition, receiver operating characteristic (ROC) analysis was performed for the most meaningful parameters. All statistical analyses were performed with GraphPad Prism 7 (GraphPad Software Inc., USA) and the PAWS Statistics 17.0.2 (SPSS Inc., USA) for Windows.

**Results**

We initially considered a total of 155 subjects. Thirty-five patients were excluded for the following reasons: n = 3 for metastatic cancer, n = 7 for hematological disorders, and n = 25 for ongoing antiplatelet or anticoagulant therapy, leaving 120 participants. Thirty-six (30%) patients died within 28 days of severe sepsis diagnosis (Group A) and twenty-three (19%) patients between days 29 and 90 (Group B). Sixty-one (51%) patients were still living at day 90 (Survivors). The demographic and clinical characteristics of the study population are reported in Table 1. There were no significant differences between groups A and B in terms of gender, age, co-morbidities (e.g., cancer, diabetes), cause of sepsis, origin of infection, and SOFA and JAAM scores. Survivors were significantly younger than patients in both groups A and B (P < 0.001 in both comparisons). Regarding traditional coagulation parameters, no significant differences were found between Group A and Group B (Table 2). D-dimer levels were significantly higher in groups A and B compared to Survivors (P = 0.030 and 0.003, respectively). ROTEM® parameters

ROTEM® parameters are described in Table 3. Both CT and CFT in the EXTEM assay were significantly prolonged in Group A compared to Group B (P = 0.041 and 0.020, respectively). The remaining EXTEM parameters (i.e., MCF and TDI) were similar between Group A and Group B. INTEM and FIBTEM assays revealed no significant differences between Group A and Group B. In the comparison between Group A and Group B vs survivors, all parameters considered in the EXTEM assay revealed a significantly hypocoagulable profile in the former two groups (Table 3).
No significant differences were found between Group A and Group B vs Survivors in the INTEM and FIBTEM assays.

**MULTIPLATE® parameters**

The MULTIPLATE® parameters are reported in Table 4. Platelet function in ADP, ASPI, and TRAP tests was significantly lower in Group A than in both Group B (P = 0.020, 0.007, and 0.005, respectively) and Survivors (P = 0.006, 0.015, and 0.004, respectively). No differences were found between Group B and Survivors. Furthermore, an ROC analysis revealed a significantly worse platelet dysfunction in Group A than in both Group B and Survivors (P ≤ 0.006 for both groups in all reagents considered) (Table 5).

**Discussion**

Sepsis-induced coagulopathy is characterized by predominant activation of the tissue factor pathway with a remarkable consumption of coagulation factors, platelet activation, and fibrinolysis [6–9,18]. However, traditional coagulation tests (i.e., prothrombin time, activated partial thromboplastin time, and platelet count) have shown several limitations in their ability to reliably...

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Table 2. Traditional Laboratory Parameters

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 36)</th>
<th>Group B (n = 23)</th>
<th>Survivors (n = 61)</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A vs. Group B</td>
<td>Group A vs. Survivors</td>
<td>Group B vs. Survivors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBCs (× 10^9/L)</td>
<td>16 ± 10.1</td>
<td>16 ± 9.7</td>
<td>14 ± 10.2</td>
<td>0.382</td>
<td>1.000</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>182 ± 81</td>
<td>205 ± 133</td>
<td>160 ± 74</td>
<td>0.560</td>
<td>1.000</td>
</tr>
<tr>
<td>PCT (ng/ml)</td>
<td>19 ± 5</td>
<td>21 ± 5</td>
<td>12 ± 35</td>
<td>0.424</td>
<td>1.000</td>
</tr>
<tr>
<td>Platelet count (× 10^9/L)</td>
<td>170 ± 57</td>
<td>183 ± 60</td>
<td>185 ± 99</td>
<td>0.340</td>
<td>1.000</td>
</tr>
<tr>
<td>INR</td>
<td>1.60 ± 1.31</td>
<td>1.53 ± 1.08</td>
<td>1.43 ± 0.44</td>
<td>0.543</td>
<td>0.870</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>32 ± 3</td>
<td>31 ± 6</td>
<td>31 ± 6</td>
<td>0.764</td>
<td>1.000</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>1510 ± 170</td>
<td>1632 ± 162</td>
<td>989 ± 336</td>
<td>0.002</td>
<td>1.000</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>4.7 ± 0.6</td>
<td>4.6 ± 1.9</td>
<td>4.7 ± 2.0</td>
<td>0.380</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or percentage. WBCs: white blood cells, CRP: C-reactive protein, PCT: procalcitonin, INR: international normalized ratio, aPTT: activated partial thromboplastin time. Group A: non-survivors at 28 days, Group B: non-survivors between days 29 and 90 after enrollment. P value < 0.05.

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Table 3. ROTEM® Parameters

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 36)</th>
<th>Group B (n = 23)</th>
<th>Survivors (n = 61)</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A vs. Group B</td>
<td>Group A vs. Survivors</td>
<td>Group B vs. Survivors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT (s)</td>
<td>89 [70–93]</td>
<td>75 [67–84]</td>
<td>70 [60–77]</td>
<td>&lt; 0.001</td>
<td>0.041</td>
</tr>
<tr>
<td>CFT (s)</td>
<td>91 [71–106]</td>
<td>83 [54–88]</td>
<td>63 [53–76]</td>
<td>&lt; 0.001</td>
<td>0.020</td>
</tr>
<tr>
<td>INTEM</td>
<td>75 [55–93]</td>
<td>67 [50–82]</td>
<td>66 [55–76]</td>
<td>0.210</td>
<td>0.650</td>
</tr>
<tr>
<td>MCF (mm)</td>
<td>65 [58–74]</td>
<td>66 [56–74]</td>
<td>69 [65–75]</td>
<td>0.019</td>
<td>1.000</td>
</tr>
<tr>
<td>INTEM</td>
<td>64 [54–71]</td>
<td>67 [56–73]</td>
<td>67 [62–71]</td>
<td>0.640</td>
<td>1.000</td>
</tr>
<tr>
<td>FIBTEM</td>
<td>25 [16–41]</td>
<td>26 [16–34]</td>
<td>30 [22–39]</td>
<td>0.130</td>
<td>1.000</td>
</tr>
<tr>
<td>TDI</td>
<td>0.42 [0.29–0.50]</td>
<td>0.41 [0.3–0.55]</td>
<td>0.49 [0.43–0.56]</td>
<td>0.001</td>
<td>1.000</td>
</tr>
<tr>
<td>INTEM</td>
<td>0.24 [0.18–0.32]</td>
<td>0.27 [0.2–0.34]</td>
<td>0.28 [0.23–0.33]</td>
<td>0.340</td>
<td>0.900</td>
</tr>
</tbody>
</table>

Values are presented as median and [IQR]. CT: clotting time, CFT: clot formation time, MCF: maximum clot firmness, TDI: thrombodynamic index. Group A: non-survivors at 28 days, Group B: non-survivors between days 29 and 90 after enrollment.
and consistently detect coagulation disorders in sepsis [1,3,18–20]. Our findings confirmed that only a high age and D-dimer among standard laboratory tests appeared to be different between non-survivors and controls.

Therefore, we investigated the use of thromboelastometry (ROTEM®) in sepsis, a promising point-of-care test that was shown to be effective as a rapid global assessment of hemostasis in whole-blood samples, allowing the assessment of each stage of the coagulation process in bleeding patients [21–24]. We also examined the potential correlation between a higher risk of short-term death and severe hypocoagulability. Finally, we assessed sepsis-induced platelet dysfunction by using impedance aggregometry MULTIPLATE®, a promising technique still under investigation in sepsis [11]. We were able to confirm that both non-survivors at 28 days (Group A) and non-survivors between days 29 and 90 (Group B) exhibited more hypocoagulable profiles compared to Survivors (i.e., longer CT, longer CFT, and reduced MCF and TDI in the EXTEM assay). These parameters have been widely studied in the literature, and each parameter measures a specific phase of the coagulation cascade which is differently influenced by coagulation factors, fibrinogen, platelets, or the fibrinolytic system [18,22–24]. However, the prognostic value of these parameters remains unclear. In fact, we previously showed that only the novel TDI — the ratio between MCF, CT, and CFT — is an independent predictor of long-term mortality owing to its ability to assess the patient's global coagulation capabilities [16]. Based on this finding, we hypothesized that increased hypocoagulability may correlate with a higher risk of short-term death and that traditional coagulation tests carry no prognostic value in non-survivors at 28 days vs 90 days. We found that non-survivors at 28 days had longer CT and CFT values in the EXTEM assay vs. non-survivors between 29 and 90 days, linking higher hypocoagulability to the risk of death within 28 days.

Some reports have indicated that alterations in hemostasis and blood coagulation may occur as early as 60 minutes after induction of endotoxemia. Sepsis-induced coagulopathies have been linked to higher endotoxin activity, increased release of biomarkers of endothelial injury, meaningful changes in the coagulation process, and higher mortality risk [25–27]. Specifically, CFT has been previously described as the most sensitive tool for the rapid detection of hypocoagulability though no differences between short and long-term mortality have been demonstrated to date [25]. Moreover, CFT relies on clotting factors and platelet function [18] and it is well established that thrombocytopenia is an important predictor of ICU mortality [28]. However, we found no differences in platelet count between cases and controls, which informed our decision to use the more accurate MULTIPLATE® device to conduct an in-depth analysis of sepsis-induced platelet dysfunction. We found that, despite similar platelet counts across groups, aggregation in the ADP, ASPI, and TRAP tests was significantly impaired in Group A compared to Group B and Survivors. Platelet function was similar in the latter two groups.

Some of our MULTIPLATE® findings have been partially described in previous studies but no data are available pertaining to

<table>
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<th>Table 4. MULTIPLATE® Parameters</th>
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<td>ADP-test</td>
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<tr>
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</tr>
<tr>
<td>ADP-test</td>
</tr>
<tr>
<td>ASPI-test</td>
</tr>
<tr>
<td>TRAP-test</td>
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</table>

Values are presented as area under the curve (AUC, AU*min) median and [IQR]. Group A: non-survivors at 28 days, Group B: non-survivors between days 29 and 90 after enrollment. ADP: adenosine diphosphate test, ASPI: arachidonic acid test, TRAP: thrombin receptor activating peptide-6 test.

<table>
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<tr>
<th>Table 5. The ROC Analysis for MULTIPLATE®</th>
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<td>ADP-test</td>
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<td>TRAP-test</td>
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</table>

Group A: non-survivors at 28 days, Group B: non-survivors between days 29 and 90 after enrollment. ROC: receiver operating characteristic, ADP: adenosine diphosphate test, ASPI: arachidonic acid test; TRAP: thrombin receptor activating peptide-6 test.
differences between long and short-term mortality \[11,29,30\]. Adamzik et al. \[11\] compared sepsis patients to post-operative patients and concluded that impedance aggregometry was a better predictor of 30-day survival than conventional biomarkers such as platelet count, although they did not assess long-term mortality. Similar results were obtained by Davies et al. \[29\] who analyzed 106 adults and reported a more significantly impaired platelet aggregation in patients with severe sepsis/septic shock (compared with SIRS/sepsis without complications) and in non-survivors at 28 days. The authors concluded that reduced platelet aggregometry responses were significantly associated with morbidity and mortality in sepsis and SIRS patients. MULTIPLATE® was shown to be a valid point-of-care test in sepsis patients with overt disseminated intravascular coagulation, a life-threatening complication that often occurs in critically ill patients \[30\]. However, no investigation discriminated between short-term and long-term non-survivors. In clinical practice, the risk stratification of mortality in adults with sepsis could be vital.

In addition, we opted to enroll all patients upon admission to ensure that early differences in coagulative profiles and platelet function among severe-sepsis subjects would be accounted for, rather than studying changes over time, which could be an interesting starting point for future investigations \[27\]. We would like to acknowledge some of the limitations of our study: i) the sample size, albeit the study population was highly homogeneous, was restricted by extensive exclusion criteria; ii) ROTEM® and MULTIPLATE® are not readily available in most health facilities; iii) this was an observational study, thus making it impossible to independently assess the causal relationship between ROTEM®/MULTIPLATE® results and outcomes; iv) the thromboelastometry method and impedance aggregometry are non-standardized tests that yield highly variable results across patients. Therefore, the present study should be considered as a hypothesis-generating effort rather than an attempt to provide definitive answers as to the clinical utility of ROTEM® and MULTIPLATE® in every-day clinical practice. Further large-scale prospective investigations are warranted to support our findings.

The present study showed that the combination of thromboelastometry and impedance aggregometry may help identifying sepsis patients at high risk of short-term death. Non-survivors at 28 days more frequently exhibited a higher level of hypocoagulability compared to non-survivors at 90 days. In particular, CT and CFT in the EXTEM assay resulted significantly prolonged and platelet aggregation was meaningfully impaired in all reagents considered in patients who died within 28 days.

Conflicts of Interest

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

Author Contributions

Annalisa Boscolo (Conceptualization; Data curation; Writing – original draft; Writing – review & editing)
Luca Spiezia (Conceptualization; Formal analysis; Investigation; Methodology)
Elena Campello (Conceptualization; Formal analysis; Methodology)
Diana Bertini (Conceptualization; Data curation)
Vittorio Lucchetta (Conceptualization; Data curation)
Eleonora Piasentini (Data curation)
Alessandro De Cassai (Conceptualization; Formal analysis)
Paolo Simioni (Conceptualization; Supervision; Validation; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) Checklist

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Paolo Simioni, https://orcid.org/0000-0002-6744-383X

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A novel approach to bedside pretransfusion identity check of blood and its components: the Sandesh Positive-Negative protocol

Sandesh Udupi¹, Kriti Puri¹,²

Department of Anesthesiology, ¹Kasturba Medical College, Manipal, ²Lady Hardinge Medical College, New Delhi, India

Background: Blood component mistransfusion is generally due to preventable clerical errors, specifically pretransfusion misidentification of patient/blood unit at bedside. Hence, electronic devices such as barcode scanners are recommended as the standard instrument used to check the patient’s identity. However, several healthcare facilities in underdeveloped countries cannot afford this instrument; hence, they usually perform subjective visual assessment to check the patient’s identity. This type of assessment is prone to clinical errors, which precipitates significant level of anxiety in the healthcare personnel transfusing the blood unit. Hence, a novel objective method in performing pretransfusion identity check, the ‘Sandesh Positive-Negative (SPON) protocol,’ was developed.

Methods: A nonrandomized study on bedside pretransfusion identity check was conducted, and 75 health care personnel performed transfusion. The intervention was performed by matching a custom-made negative label with blood component with the positive label of the same patient available at bedside who was about to receive transfusion.

Results: In total, 85.3% of the subjects were anxious while performing pretransfusion identity check based on the existing standard practice. After the implementation of the SPON protocol, only 38.7% experienced either mild, moderate or severe anxiety. The overall level of satisfaction also increased from 8.0% to 38.7% and none were dissatisfied. Although only 9.3% were dissatisfied about the existing practice, approximately 70.7% felt the need for a better/additional protocol. Clerical error was not observed.

Conclusions: The SPON protocol is a cost-effective objective method that reduces anxiety and increases satisfaction levels when performing final bedside identity check of blood components.

Keywords: Blood component transfusion; Blood safety; Errors; Hemovigilance; Mistransfusion; Novel intervention; Organization and administration; Prevention and control; Standards.

Introduction

Transfusion of blood and its components occasionally results in serious hemolytic reactions due to the transfusion of wrong blood type, which is considered a human clerical error. This type of error may occur at the initial stages of blood collection, labeling, grouping, and transportation, or more importantly, this error may possibly be observed when a healthcare personnel fails to perform final bedside identity check between the patient and blood component unit before transfusion. The World Health Organization has established several policies and guidelines for a safe blood transfusion [1].

Pretransfusion final identity check, which ensures the transfusion of the right unit for the right patient, is best achieved by using various electronic transfusion management...
However, in healthcare facilities that cannot afford these expensive instruments, identity check is performed by the healthcare personnel initiating the transfusion (transfusionist) by visually matching patient's details available at bedside with the compatibility label attached to the blood component unit and transfusion prescription \[1,6\]. This is a subjective and self-confirmatory method performed based on the transfusionist's subjective clinical assessment. Occasionally, clerical errors due to stress, increased workload, or mere negligence during this process, resulting in fatal and legal consequences, can be observed. Hence, the transfusionist may experience a significant level of anxiety. Therefore, the use of a cost-effective objective method would be beneficial. Hence, a novel ‘Sandesh Positive-Negative (SPON) protocol’ for checking the patient’s identity with the blood components before transfusion was developed and evaluated.

This study aimed to compare the SPON protocol with the standard protocol for the final identity check of blood components at bedside to ensure the transfusion of the right blood unit for the right patient. The primary study hypothesis was to compare the two protocols with respect to the transfusionists’ anxiety and satisfaction levels. The secondary hypothesis was to observe the chances of avoidable clerical errors/near-miss events of mismatched transfusion. Hence, a novel negative label was created that would match with the characters of a positive label only if it belonged to the same patient.

**Materials and Methods**

**Study population**

This study was approved by the Kasturba Medical College and Hospital Institutional Ethics Committee (IEC-457/2017). The study was also registered in the Clinical Trial Registry of India (CTRI/2017/10/010002 [Registered on 04/10/2017], principal investigator – Dr. Sandesh U). All subjects provided written informed consent for inclusion in the study. Subjects with the following characteristics were included in the study: (a) a healthcare personnel authorized to perform blood component transfusion (if required for the patient as advised by the consultant doctor) and (b) who had performed at least 50 transfusions earlier in his/her healthcare profession. A total of 75 subjects were enrolled in the study. They were further divided into 3 groups of 25 based on their job profile: (1) doctors/consultant anesthesiologists, (2) postgraduate students of anesthesiology and intensive care, and (3) nurses. The procedure in the SPON protocol was explained and also demonstrated with hands-on training experience by allowing them to perform the procedure using sample labels. The procedure was demonstrated several times until each of the subjects had completely and accurately performed the protocol.

**Standard protocol**

The blood component unit arrives at the site of transfusion along with the compatibility report and label. At bedside, initially, the transfusionist visually matches the blood unit with the compatibility label and report and subsequently further matches all of these with the patient’s details (present on the patient’s wristband/ and patient’s hospital records). Once all the details are matched and the blood component is considered as the ‘right unit’ for the ‘right patient,’ the transfusionist affixes his/her signature on the compatibility form confirming that the identity check is properly performed. Furthermore, this entire process executed by the transfusionist is cross-checked by another personnel (termed ‘double check’), and after the cross-checking, the transfusion is initiated.

**Sandesh Positive-Negative (SPON) protocol**

It basically comprises matching two labels having patient’s details at bedside of a patient who is about to receive transfusion. The protocol consists of the following components (Fig. 1):

1. **Positive label**

   Typically, each patient admitted to any hospital is provided with a distinctive label for identification with details regarding the pa-
tient’s name, age, gender, ward, hospital unique identification number, and other details. The positive label is the similar label that is available at the patient’s bedside at the site of transfusion (Fig. 1A, a).

**Negative label**

It is a custom-made label with four rectangular punched-out spaces/gaps (Fig. 1A, b). It has exactly similar dimensions as that of the positive label. In this label, patient details similar to the positive label could be printed. Hence, when patient details are printed on this negative label, due to gaps, some of the characters corresponding to these gaps will not be printed. The unprinted/blank negative label is made available at the blood bank so that when a request for blood or its component unit is received, patient’s details are printed on the negative label concurrently along with the routinely printed compatibility label and compatibility report using an integrated software program.

**SPON label strip**

It is a customized label strip that has places to paste two labels and affix a signature (Fig. 1A, c). The positive and negative labels, label strip, and compatibility label are all sticky labels that can be peeled off and pasted on to another surface.

Hence, the blood component is sent to the site of transfusion along with the negative label, SPON label strip, compatibility report, and compatibility label.

At the site of transfusion, upon receipt of blood component with the abovementioned items, the transfusionist initially performs the standard protocol; subsequently, the SPON protocol is performed.

**Steps in the SPON protocol**

Step 1: Two positive labels that are available near the patient are pasted on spaces provided in SPON label strip (Fig. 1).

Step 2: Subsequently, the negative label is peeled off, aligned correctly on top of one of the positive labels, and pasted over it. This now forms the combined positive-negative (P-N) label (Fig. 2). The gaps in the negative label will be filled by characters from the underlying positive label. Hence, the characters in the combined P-N label form a continuum by characters partly from the negative label and remaining from the underlying positive label (corresponding to the gaps in the negative label). This continuum of characters will be accurate and comprehensible only when both the negative label on top and underlying positive label belong to the same patient.

Step 3: The combined P-N label is further compared with the adjacent second positive label and ensured that both P-N label and second positive label match exactly with each other. This is again possible only if both the positive and negative labels belong to the same patient (Fig. 2).

Step 4: Subsequently, the transfusionist affixes his/her signature in the space provided in the label strip to confirm the authenticity of the properly performed SPON protocol. The negative label can also be made light colored, which makes its characters in the combined P-N label stand out and aid in better comparability.

Step 5: Furthermore, the whole SPON label strip containing the combined P-N label, positive label, and signature is attached to the patient’s record file for future reference.

After completing these steps, the transfusion is initiated.

The transfusionist subsequently answered a written questionnaire about performing a new protocol, and the results were interpreted based on their responses. The questionnaire included the following parameters: anxiety about blood transfusion, reason for anxiety, satisfaction about the existing standard protocol, need for new protocol, difficulty and workload in performing the new protocol, and the anxiety and satisfaction after the implementation of the new protocol. Anxiety level was measured based on the perception of anxiety by the transfusionists as none, mild, moderate, or severe.

Satisfaction levels were assessed based on the perception of satisfaction as dissatisfied, satisfied, and highly satisfied.

![Fig. 2. Steps of SPON protocol. (A) Process of alignment of the negative label on top of the positive label. (B) The Sandesh Positive-Negative label strip with the positive label, combined positivenegative label, and signature.](https://doi.org/10.4097/kja.19402)
In addition to the above parameters, the following were also noted: (a) number of times identity check was performed with anxiety about the existing protocol, which was quantified as either once or twice and several times; (b) whether the transfusionists properly performed the identity check as cross-checked by another personnel (double checking) after their initial safety check; (c) number of near-miss events that occurred in a transfusionist's profession earlier ('near-miss' events were considered errors that could result in the transfusion of an incorrect blood component if left undetected, but these errors were recognized before the transfusion was performed [7]); (d) amount of workload perceived by the transfusionist while performing the new protocol, quantifiable as nothing, manageable/minimal, moderate, or excessive extra work; and (e) whether the new protocol was considered worthy and whether it would be recommended for future implementation on a standard basis.

It is further emphasized that the SPON protocol was performed in addition to and after the standard protocol. This was performed on purpose because bypassing the existing standard protocol would have raised serious questions about ethical issues and patient safety as the new protocol was experimental and was being implemented for the first time.

**Statistical analysis**

Anticipating 47% discordant pairs in anxiety and satisfaction before and after the implementation of the new protocol, with 95% confidence level and a power of 80%, a minimum of 68 subjects were required in this study. Hence, 75 subjects who met the inclusion criteria were enrolled in this study.

Data was summarized using descriptive statistics. Comparisons before and after the implementation of the new protocol were performed using McNemar’s test and the chi-squared tests. A P value of < 0.05 was considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 15 (SPSS South Asia, India).

**Results**

A total of 85.3% (64/75) of the subjects were anxious about the process of blood transfusion with reference to the existing standard protocol used to check patient’s identity (Table 1) due to fear of complications of mistransfusion. Moreover, in their professional career, 72.0% (54/75) of the transfusionists had near-miss events at least once, 14.7% (11) twice, and 13.3% (10) three or several times. Furthermore, the identity check of approximately 64.0% did not undergo cross-examination by a second personnel.
(double checking). Hence, approximately 69.3% (52/75) themselves performed the identity check twice or several times. Moreover, although only 9.3% (7/75) were dissatisfied about the existing protocol, approximately 70.7% (53) felt the need for a new/better or an additional protocol. After the implementation of the SPON protocol, only 38.7% (29/75) experienced any degree of anxiety (P = 0.001 in consultants, P = 0.001 in trainees, P = 0.012 in nurses). However, in total subjects, there are no differences with respect to the distribution of anxiety levels. The proportion of subjects being highly satisfied increasing from 8.0% to 38.7% (P = 0.011), and none of them were dissatisfied (Table 1). Additionally, 48.0% felt minimal but manageable extra work in performing the protocol. Moreover, 84.0% (63/75) considered the new protocol worthy, and 89.3% (67/75) recommended for its implementation on a regular basis (Table 2). None of the subjects had experienced difficulty in performing the protocol, and clerical error was not observed during the study.

**Discussion**

Transfusion of blood and its components is a complex multi-step process involving several diverse healthcare professionals, namely, doctors, laboratory technologists, and nurses apart from donors and recipients. Accordingly, errors can occur during any of these steps starting from the initial stages of blood collection until transfusion, causing fatal complications. Contributory causes for these errors are mostly due to the widely recognized ‘human factors’ such as increased workload, slips and lapses, fatigue, lack of attention, and taking shortcuts and omission of essential steps [7]. Patients are at a higher risk of a wrong blood transfusion than any other transfusion-related complications [8,9]. This type of error is frequently observed at the patient’s bedside just prior to the transfusion due to inappropriate identity check [10–13]. Similarly, in hospital areas requiring many blood components (e.g., large-sized wards, intensive care units [ICUs], and where several operating rooms are situated in one complex), the number of components arriving is significantly higher compared to hospital areas not requiring blood components. Often, they may have been ordered and expected simultaneously at close intervals for two or more patients positioned nearby. Hence, there are chances that the healthcare personnel transporting them may accidently deliver it to the wrong operating room/ward, probably leading to mis-transfusion.

These potentially serious errors can nearly be eliminated by removing the manual steps/human factors and introducing certain tools, for example, patient identification bracelets with barcodes and barcode readers, radio-frequency identification devices, automated analyzers in laboratories, or mechanical and electronic locks that provide safe end-to-end electronic control across the whole transfusion process [3,4,5,10]. However, in healthcare facilities that cannot afford these expensive instruments, the standard method of identity check is performed by the transfusionist by visually matching the patient’s details with the compatibility report and compatibility label (attached on the blood component) [1]. This process is completely subjective as it is solely based on the transfusionist’s assessment; as a result, the transfusionist may perform the identity check more than once. Moreover, considering that the procedure is purely subjective, clerical errors are significantly possible due to various factors described earlier. Occasionally, the compatibility label is only matched with the compatibility report and is not matched with the patient’s identity details on the wristband or at bedside. Considering that both the compatibility label and report are generated by the same laboratory computer, the two will always match even if wrong blood component is being transfused. All these factors result in a significant level of anxiety and dissatisfaction in the transfusionist. Hence, to address the need for an objective method that is not only practical and simple but also inexpensive, the SPON protocol was developed and evaluated.

Most of the transfusionists were anxious about the process of transfusion with the existing standard protocol (Table 1). The major reason for this anxiety was the fear of mistransfusion due to judgmental errors. The most common anticipated serious consequences of these errors were the fear of losing the patient’s life (44.0%) and legal consequences (30.7%). Awareness regarding legal complications was more common in consultants than in postgraduate students and nurses. Due to the significant level of anxiety regarding clerical errors, approximately 69.3% of the subjects

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### Table 2. Subjects’ Opinion regarding Extra Work, Worthiness, and Recommendation about the New Protocol

<table>
<thead>
<tr>
<th>Extra work</th>
<th>None</th>
<th>Manageable/minimal</th>
<th>Moderate</th>
<th>Excessive</th>
<th>Worthy</th>
<th>Not worthy</th>
<th>Cannot say</th>
<th>Recommendation of the SPON protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>39</td>
<td>36</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>0</td>
<td>12</td>
<td>67 (89.3)</td>
</tr>
<tr>
<td></td>
<td>52.0</td>
<td>48.0</td>
<td>0.0</td>
<td>0.0</td>
<td>84.0</td>
<td>0.0</td>
<td>16.0</td>
<td>9 (12.0)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
admitted having performed the identity check twice or several times. Moreover, although cross-examination of the identity checked by a second personnel (double check) was recommended and considered as part of the standard procedure, the identity check of approximately 64.0% (48/75) of the transfusionists did not undergo cross-examination. The common reason for this was the lack of healthcare personnel available at the time of cross-examination. Furthermore, evidence regarding the safety of performing bedside check by one or two healthcare staff does not exist [6]. Hence, 70.7% (53/75) felt the need for a new/better or an additional protocol for identity check.

The P-N label works based on the lock and key principle where only a unique key would fit into the respective keyhole of its corresponding lock to unlock it. In the SPON protocol, the P-N label is a proof of compatibility as the negative label will match with its corresponding positive label only if it belongs to the same patient. Although most of the steps in the SPON protocol are objective, the final step requires visual confirmation and judgment. Even then, it is significantly easier to determine any disparity between the positive and combined P-N label as they both lie adjacent to each other (Fig. 2). It is easier to compare the two items precisely when placed nearby rather than farther away. After the implementation of the protocol, the proportions of the transfusionists who rated the anxiety as mild, moderate, or severe decreased considerably from 85.3% to only 38.7%. Moreover, none of the subjects were dissatisfied with an overall increase in satisfaction levels.

Adding an extra phase to an existing protocol seemed to increase the transfusionists’ workload as 48% felt that the new protocol added extra, but minimal and manageable, work. Nevertheless, 84% felt that the extra effort was absolutely worthwhile (Table 2). They believed that the benefits of this minimal extra effort outweigh far greater than the consequences of a mistransfusion with respect to mortality and legal concerns. The SPON protocol was proven to be simple and easily comprehensible since none of the subjects had experienced difficulty in performing the protocol.

Clerical errors were not observed during the study probably because the overall incidence of clerical errors has drastically decreased over the years due to the comprehensive reporting of incidents and implementation of standard policies and the subjects were extra vigilant due to their conscious enrolment in the study. However, approximately 28% (21) reported to have experienced near-miss events in their profession more than once, causing a significant level of anxiety. ‘Near-miss’ events comprise a third of all SHOT reports, which was comparable to our study [7,14]. These were mainly observed in the ICU/general ward where blood components were erroneously placed near a different patient or in a common area. It was also noted that although those events were promptly avoided with the existing standard protocol itself, the subjects felt that a new protocol would have reduced the anxiety they experienced during those events. Hence, although the SPON protocol may be comparable to the standard protocol in terms of avoiding clerical errors, it is absolutely superior in terms of reducing anxiety and improving satisfaction levels. Therefore, most of the subjects recommended the protocol for implementation on a standard basis.

Traditional double checking performed by two medical personnel is also considered a subjective way that is dependent on the assessment of the second personnel; hence, when double checking is performed, objective confirmation is not provided. Hence, the SPON protocol performed by one transfusionist may provide an objective confirmation over traditional double checking. However, an adverse effect as a result of the omission of the standard double checking can be possibly observed, leading to errors and ethical concerns. Hence, the SPON protocol would yield superior results if used as an additional rather than a replacement method to the existing standard method, which also formed the basis for designing this study.

However, the study had the following limitations. First, the study could not be conducted as a randomized cross-over study to avoid the significant period effect and carryover effect. Second, this study comprised a small sample size; hence, clerical errors were not clearly evaluated considering that the estimation of errors required a large sample size (in this study, the incidence of clerical errors was significantly low even with the existing standard protocol). Furthermore, the implementation of any new method on a large scale involves ethical issues, specifically if it involves errors leading to significant morbidity. Third, clerical errors were not observed in the present study sample, which is possibly due to the conscious enrolment of subjects for the new protocol; hence, the subjects were extra vigilant.

The SPON protocol is more confirmatory than the existing protocol due to its dual subjective and objective nature indicating the right blood for the right patient. Importantly, evidence regarding the appropriate performance of identity check exists as the final label strip is attached to the patient’s hospital record file. This is considered beneficial in addressing possible medicolegal concerns or litigations in the future as erroneous transfusion amounts to medical negligence, resulting in punishment and warranting huge monetary compensation. Moreover, the cost of this additional protocol per patient was estimated to be merely 0.4 Indian National rupee/0.0058 US dollar/0.0044 Pound Sterling [15]. Since it does not require any additional infrastructure and manpower, it can be easily implemented and possibly be incorporated as a standard operating protocol for safe transfusion by regulatory authori-
ties specifically in Third World countries. It can also be a major database used in the hemovigilance systems of any country [9]. Therefore, the 'SPON protocol' is a simple and cost-effective objective method when performing final bedside identity check of blood components for an improved transfusion practice.

**Acknowledgements**

The authors acknowledge the cooperation from the Departments of Transfusion Medicine and Information Systems of Kasurba Medical College and Hospital, Manipal, Karnataka, India. The Transfusion Medicine Department contributed to the organization of label printing. The Department of Information Systems contributed to the integration of computer software.

**Conflicts of Interest**

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

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**References**


Introduction

Sugammadex is a prime antagonist of aminosteroidal neuromuscular blocking agents (NMBAs), especially rocuronium; However, before introducing sugammadex, it should be noted that the indirect mechanism of antagonism of the rocuronium-induced neuromuscular block has a ceiling effect, and is limited by the depth of the neuromuscular block at the time of reversal [1].
In the clinical setting, recovery of neuromuscular blockade is monitored through responses of the innervated muscle under indirect neuronal stimulation, particularly that of the ulnar nerve at the wrist level and the adductor pollicis muscle [2]. Patients with partial neuromuscular block usually show a train-of-four (TOF) ratio of < 0.7. TOF ratio of > 0.9 by mechanomyography or an electromyography-type monitor or > 1.0 by an acceleromyography-type monitor are considered as complete recovery [2]. However, these definitions were mostly established when neuromuscular blockade recovery was done by anticholinesterases. During blockade with nondepolarizing NMBAs, TOF fading occurs as a result of presynaptic cholinergic autoreceptor activity, which is influenced by concentrations of NMBAs and acetylcholine (ACh) at the neuromuscular junction [3]. Anticholinesterase administration was the main method of antagonism of neuromuscular blockade which cause an increase in ACh at neuromuscular junctions, which thereby outcompetes rocuronium at postsynaptic nicotinic acetylcholine receptors (nAChR) [4,5]. In contrast, sugammadex-induced antagonism is unrelated to ACh release or cholinergic activity [1]. Sugammadex directly encapsulates and inactivates rocuronium in a 1:1 ratio at the molecular level [6,7]. As such, we assumed that the TOF ratio recovery pattern by sugammadex might be different from those of anticholinesterase-induced recovery from neuromuscular blockade because sugammadex has no effect on ACh release or metabolism at the neuromuscular junction [1]. During sugammadex-induced neuromuscular recovery, the TOF ratio recovers to nearly 1.0 immediately after injecting sugammadex. However, patient complaints of muscle weakness have been reported even when extubation is performed after securing a TOF ratio of > 0.9. Indeed, it has been reported on several occasions that the TOF ratio recovery preceded twitch recovery in clinical settings during sugammadex-induced neuromuscular recovery [8–10].

As such, we hypothesized that at different doses of sugammadex for neuromuscular blockade reversal, rocuronium will be eliminated at different rates from neuromuscular junction, and the different affinities of rocuronium to the pre- and post-synaptic AChRs may affect recovery of both T1 and the TOF ratio, which may be hindered during anticholinesterase-induced recovery from neuromuscular blockade. The primary objective of this study was to assess recovery progressions of T1 and the TOF ratio after administering different doses of sugammadex, and to compare the results obtained with those at spontaneous recovery. The secondary objective was to examine inter-group differences of TOF ratio recovery at the same T1 twitch tension during recovery from rocuronium-induced neuromuscular blockade.

Materials and Methods

Basic study design and sample preparation

This ex-vivo study protocol was approved by the Ethics Committee of the Laboratory of Animal Research of the Asan Institute of Life Science (Seoul, Korea) on July 1, 2017 (Protocol No. 2017-13-114). All animals were bred at a constant ambient temperature of 22°C under a regular diurnal cycle, and food and water were supplied ad libitum. The phrenic nerve-hemidiaphragm tissues were immersed in Krebs buffer solution (120 mM NaCl, 2.5 mM CaCl₂, 4.7 mM KCl, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 25 mM NaHCO₃, and 11 mM α-D-glucose) and maintained at 35°C with continuous bubbling of a mixture of 95% O₂ and 5% CO₂ to ensure tissue viability throughout the whole study. The sizes and weights of the tissues were measured and compared between groups (Table 1). In all experiments, sugammadex, rocuronium (Bridion® and Esmeron®, respectively; MSD Korea, Korea), and alfaxalone (Alfaxan®; Careside Co. Ltd, Korea) were used.

Protocol for the main experiment

Sixty male Sprague-Dawley rats weighting an average of 354.8 ± 36.9 g (range 298.5–438.9 g) were used in the study. The rats were anesthetized with an intraperitoneal injection of 10 ml/kg of alfaxalone. The thoracic cages were immediately isolated and phrenic nerve-hemidiaphragm tissues were obtained. The tissues were

| Table 1. Characteristics of Rats and Tissue Specimens |
|---------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                                | Control           | SGX               |
|                                | 0.75 (n = 10)     | 1 (n = 10)        | 2 (n = 10)        | 4 (n = 10)        | 8 (n = 10)        |
| BW (g)                         | 296.4 ± 13.7      | 303.7 ± 16.9      | 314.7 ± 16.1      | 306.0 ± 14.9      | 297.2 ± 16.6      |
| wWt (mg)                       | 202.0 ± 11.9      | 178.1 ± 17.9      | 191.9 ± 12.9      | 180.3 ± 9.7       | 176.8 ± 15.2      |
| Size (cm²)                     | 2.0 ± 0.1         | 1.8 ± 0.01        | 1.9 ± 0.1         | 1.8 ± 0.1         | 1.8 ± 0.6         |

Data are expressed as the mean ± SD. SGX: sugammadex, BW: body weight of the rat, wWt: wet weight of the hemidiaphragm. Size: size (width x length) of the hemidiaphragm. *0.75, 1, 2, 4, or 8 times equimolar doses of rocuronium to produce > 95% T1 depressions, respectively. There were no statistically significant differences between groups (P > 0.05).

https://doi.org/10.4097/kja.19278
fixed to a frame with electrodes and subsequently immersed in a 100 ml organ bath containing 75 ml of oxygenated Krebs buffer solution. For each specimen, the tendinous portion of the diaphragm was connected to a Grass FT03 Force Transducer (Grass Technologies, USA), and a resting tension of 40 mN was applied. The phrenic nerve was fixed to a platinum bipolar electrode and stimulated using a Grass S88 Stimulator (Grass Technologies, USA). Regarding TOF simulation, supramaximal stimulation was delivered using a square wave pulse of 0.2 ms at 20-second intervals at 2 Hz for a total duration of 2 s. All waveforms were displayed and stored using the PowerLab 4/26 data acquisition system (AD Instruments, Australia) and Lab-Chart 7 software (AD Instruments, USA).

The phrenic nerve-hemidiaphragm tissues were randomly allocated to either a control group (washout) or one of five groups of different sugammadex doses (0.75, 1, 2, 4, or 8 times equimolar doses of rocuronium to produce > 95% T1 depressions; SGX0.75, SGX1, SGX2, SGX4, and SGX8, respectively) using random numbers generated by Microsoft Office Excel 2013 (Microsoft, USA). We sorted the groups into two categories: a high-dose group, with sugammadex at ≥ 2 times the equimolar dose of rocuronium; and a low-dose group, with sugammadex equal to or less than the equimolar dose of rocuronium. Twitch tensions and TOF ratio were serially monitored during a 30 min-stabilization time. After the stabilization period, 400 µg rocuronium was added to the organ bath. Subsequently, 200 µg booster doses of rocuronium were added when the five consecutive T1 depressions were either ≤ 3% of the previous T1 twitch tension, or 10 minutes after the previous dose. Booster dosing was stopped when T1 depression of ≥ 95% was achieved. The loading dose was set as the amount that produced no change in T1 twitch tension but changed the TOF ratio within 3% of that before the loading dose. Booster doses were set as the level of the first booster that produced a change of the T1 twitch tension, and the total numbers of boosters administered was ≤ 10. The study protocol is summarized in Fig. 1.

The concentration of rocuronium required to obtain a reduction of T1 of > 95% was noted in the control and all sugammadex groups. For the comparisons, rocuronium dose-responses were plotted, regression curves obtained, and group-wise comparisons of the values performed. TOF ratios were obtained while monitoring T1 depression, and the regression curves were compared among the groups. Following that, inter-group progressions of the TOF ratios by % recovery of the T1 at each different sugammadex dose were compared among the groups.

Fig. 1. Study protocol. SGX: sugammadex, TOF: train-of-four, T1: first twitch tension of TOF, ROC: rocuronium.

Statistical analysis

The sample size was calculated based on the previous experiment and pilot study, which suggested that 10 samples per group were sufficient at α = 0.05, power = 0.80, and a dropout rate of 10%. Results are expressed as mean ± SD. All doses are expressed as µM. Statistical analysis was carried out using SPSS ver. 13.0 software (IBM Corp., USA). Recovery data were plotted by fitting nonlinear regression curves to the group data. An equation model was selected when the R² > 0.8 by using curve estimation in SPSS. To describe recovery of T1 and the TOF ratio, the following equation was used: y = Ωx + b; where y represents TOF ratio progression, x represents T1 recovery, and Ω represents the slope of the regression curve (R² = 0.87). For simultaneous group-wise com-
parison of recovery progression of T1 and the TOF ratio by time, a variable (TOFR/T1 product; which contained data of TOF ratio over T1 at specific time-point) was calculated using the following equations: \( y = \lambda x \), or \( y = \lambda \cdot 1/x \), where \( y \) and \( x \) represent the TOFR/T1 product and time, respectively, while \( \lambda \) represents the slope of the regression curve (\( R^2 = 0.91, 0.83 \) in the low- and high-dose groups, respectively). Different \( \Omega \) and \( \lambda \) values correspond to the speed of T1 recovery to > 95%, TOF ratio to > 0.9, or speed of increment of decay of the TOFR/T1 product. The mean group values of \( \Omega \) and \( \lambda \) were compared using the Mann Whitney U test. Statistical significance was accepted at P values of < 0.05.

Results

The specimen sizes and weights were similar in the six groups (Table 1). In the control, SGX0.75, and SGX1 groups, reappearance of T1 before the TOF ratio (Figs. 2A, 2B, and 2C) and of T2, T3, and T4 was observed. However, in the SGX2, SGX4, and SGX8 groups, simultaneous reappearance of T1 and T4 was observed and a TOF ratio of ≥ 0.7 was obtained from the start of recovery (Figs. 2D, 2E, and 2F). Inter-group comparison was conducted on the TOF ratio progression by T1 recovery. Based on the results in Fig. 2, the slopes (\( \Omega \)) of the control, SGX0.75, and SGX1 groups (Fig. 3A) were steeper than those of the SGX2, SGX4, and SGX8 groups (Fig. 3B). The combined T1 recovery and TOF ratio was expressed as a single variable (TOFR/T1 product), which was plotted against time (Fig. 4). In the control, SGX0.75, and SGX1 groups, regression curves were fitted using the following equation: \( y = \lambda x \); where \( y \) represents the TOFR/T1, \( x \) represents the recovery time with 5% T1 recovery as the zero point, and \( \lambda \) represents the slope (Fig. 4A). In these groups, no statistically significant differences in \( \lambda \) were observed. In the SGX2, SGX4, and SGX8 groups, the regression curves were fitted using the following equation: \( y = \lambda \cdot 1/x \), where the variables represent the same parameters as those for the equation, \( y = \lambda x \) (Fig. 4B).

Discussion

This ex-vivo experiment demonstrates that the recovery pat-
Fig. 3. T1 vs TOF ratio progression in all groups. The nonlinear regression equation was estimated and selected at R2 of > 0.7; the differences of slope were compared. In SCX groups, 0.75, 1, 2, 4, or 8 times equimolar doses of rocuronium to produce > 95% T1 depressions was treated, respectively. There were no statistical differences between the control, SGX0.75, and SGX1 groups. In the SGX2, SGX4, and SGX8 groups, the slopes were lower compared to those in the other group. Ω: slope constant for each regression curve, SGX: sugammadex, TOF: train-of-four, T1: first twitch tension of the TOF, TOFR: TOF ratio.

Fig. 4. The relationship between T1 and the TOF ratio was converted to a variable (TOFR/T1 product) and expressed as a function of time. A) TOFR/T1 products of control (filled circle symbol, solid line), SGX0.75 (diamond symbol, dash line), and SGX1 (triangle symbol, dash-dot line) groups. B) TOFR/T1 products of SGX2 (open circle symbol, solid line), SGX4 (triangle symbol, dash line), and SGX8 (square symbol, dash-dot line) groups. In SCX groups, 0.75, 1, 2, 4, or 8 times equimolar doses of rocuronium to produce > 95% T1 depressions was treated, respectively. The regression equations of SGX0.75 and SGX1 were in accordance with those of the control group (linear pattern; y=λ*x + b). The SGX2, SGX4 and SGX8 groups, were most suitably expressed by exponential decay (y=λ*1/x + 1), with significant differences compared to the control, SGX0.75, and SGX1 groups. λ: slope constant for each regression curve, SGX: sugammadex, TOF: train-of-four, T1: the first twitch tension of TOF, TOFR: TOF ratio.
neuromuscular blockade, the TOF fade and TOF ratio are both considered phenomena related to presynaptic neuronal nAChRs [3,14,15]. A recent study reported that these phenomena are related to the postsynaptic receptor type [15]. Those authors conducted an in-vivo experiment; the TOF fade occurred only under blockade of the postsynaptic nAChRs with α-bungarotoxin (α-BTX) or α-conotoxin, but not under that of the presynaptic nAChR with specific blockers alone. Moreover, co-administration of α-BTX or α-conotoxin during presynaptic nAChR blockade resulted in a prominent TOF fade. Other studies reported that the presynaptic nAChR regulates the amount of ACh per neural stimulus [15,16]. Faria et al. [15] reported that blockade with dihydro-β-erythrodine (DhβE) was effective in decreasing the level of prejunctional ACh release, which was consistent with the findings from another study using a cell culture model. Decrease of ACh release causes the onset of a neuromuscular blockade, which was slow under blockade of only the postjunctional nAChRs, but accelerated under that of prejunctional AChRs with DhβE [17]. Therefore, the presynaptic and postsynaptic actions of NMBAs on nAChRs affect the efficacy of neuromuscular blockade [18]. Considering these results, the relationship between pre- and postsynaptic receptor function is an important determinant of the TOF fade and the TOF ratio. The conventional strategy for neuromuscular block reversal with anticholinesterase administration is not capable of eliminating NMBAs at the neuromuscular junction, leading to prolonged neuromuscular blocking activities after the initial administration of anticholinesterase. The TOF fade and the TOF ratio are prominent for the duration of NMBA action at the neuromuscular junction. This causes rapid transfer of NMBAs across the neuromuscular junction. We obtained similar results in the low-dose groups to that of spontaneous recovery. In Fig. 3A, as the TOF ratio recovered in parallel with T1 recovery and showed prominent TOF fade in the low-dose group, y-axis values (TOF ratio) often start low and converge at 1.

In contrast, TOF fade was attenuated and the TOF ratio was high even in the early recovery of T1 in the high-dose group. As such, the slopes of regression curves, Ω, of low-dose groups were steeper than those of high-dose groups. In Fig. 4, we demonstrated the simultaneous progression of % T1 recovery and the TOF ratio by time. We generated one value (TOFR/T1 product) by using T1 recovery and the TOF ratio, which were converted by % value. In the low-dose group, as the T1 recovery preceded the TOF ratio, TOFR/T1 was ≤ 1. As such, it was well-represented by the equation of y = λx. In contrast, those in the high dose group were ≥ 1 and showed a decay pattern, because TOF fade was attenuated and the TOF ratio was higher than T1 recovery.

Our study has several limitations. First, we conducted an ex-vivo experiment and disregarded the pharmacokinetic component of rocuronium action, since the phrenic nerve-hemidiaphragm tissue specimens were examined in an organ bath filled with Krebs buffer solution. The overall recovery time to > 95% T1 was > 30 minutes in the low-dose group and was shortened to < 15 minutes in the high-dose group. In clinical settings, however, the recovery time is ≤ 5 minutes considering the dose of sugammadex used. Reports have indicated that administration of 2 mg/kg sugammadex for moderate neuromuscular blockade and 4 mg/kg for deep neuromuscular blockade achieved recovery times of ≤ 3 and 5 minutes to a TOF ratio of > 0.9, respectively [20–22]. The discrepancies of recovery patterns between the in-vivo and ex-vivo approaches suggest that the results should be interpreted differently considering that NMBA-induced neuromuscular blockade is fully and rapidly recovered in clinical settings, which might hinder our results make the blockade disappeared without notice. As such, although the postoperative residual block is still a problem, even in the new era of sugammadex-induced recovery from a neuromuscular block [23,24], we should cautiously judge the clinical implications of the findings of the current ex-vivo study. Second, this study focused on the nicotinic AChR subtype at the presynaptic and postsynaptic junctions. Sugammadex has no action at the neuromuscular junction, and rocuronium has no action on the other receptors at the neuromuscular junction; this study only focused on the nAChRs, which are the primary action site of ACh and NMBAs during neuromuscular blockade. However, as we described above, several receptors modulate ACh release in different...

https://doi.org/10.4097/kja.19278
environments [12,13], and we tried to maintain a consistent environment and neural stimulation throughout the study period. We used TOF stimulation of four stimuli of 2 Hz supramaximal stimulation, which is the same mode used for clinical neuromuscular monitoring. The method of obtaining the phrenic nerve-hemidiaphragm tissue specimen had the disadvantage of temporary hypoxia and damage to the tissue specimen during preparation due to thorax extraction from the rat. To minimize these drawbacks, we made attempts to oxygenate the rat, to remove the thorax immediately after the aorta was cut, and then performed trimming of the specimen in a petri dish containing Krebs buffer solution aerated with a mixture of 95% O$_2$ and 5% CO$_2$.

In conclusion, a high dose of sugammadex rapidly reversed the neuromuscular block induced by rocuronium. However, the recovery pattern of the TOF ratio differ according to the dose of sugammadex, particularly when the amount of sugammadex is high enough compared to that of rocuronium used. In that condition, a high TOF ratio may be achieved even without full recovery of the T1 twitch tension. The TOF ratio alone might be insufficient to indicate full recovery of neuromuscular blockade without full recovery of the T1 twitch. Therefore, clinicians should use an appropriate dose of sugammadex and wait for full recovery of both the TOF ratio and T1 twitch.

Conflicts of Interest

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

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Heyran Choi (Data curation; Formal analysis; Investigation; Resources; Writing – original draft; Writing – review & editing)
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References


https://doi.org/10.4097/kja.19278


Neurolytic abdominal wall blocks with alcohol for intractable gastrostomy site pain in a cancer patient
-a case report-

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Background: There have been reports of neurolytic transversus abdominis plane (TAP) block using different agents such as alcohol or phenol for the treatment of chronic abdominal pain caused by malignant abdominal wall invasion. However, to date, there have been no reports on neurolytic abdominal wall blocks for pain with non-cancer-related origin in cancer patients.

Case: We performed subcostal TAP neurolysis using ethanol in a patient with esophageal cancer with constant pain at the site of gastrostomy. After neurolysis, the patient’s overall pain decreased, with the exception of pain in the medial part of the gastrostomy site. We performed additional rectus sheath neurolysis using ethanol for the treatment of continuous pain at the medial site, and the effect of neurolysis has persisted for over 4 months.

Conclusions: Alcohol-based TAP neurolysis and rectus sheath neurolysis provide effective pain control in a cancer patient with chronic treatment-related pain involving the abdominal wall.

Keywords: Abdominal wall pain; Cancer pain; Neurolytic peripheral block; Rectus sheath block; Regional anesthesia; Transversus abdominis plane block.
tempted TAP neurolysis using alcohol for the management of pain due to advanced cancer involving the abdominal wall, and another similar case [6] reported the use of phenol for TAP neurolysis. However, there has not been a case report describing neurolysis performed on the rectus sheath, and cases of alcohol-based neurolysis on the abdominal wall plane for management of non-cancer pain in cancer patient.

In this case report, we describe the case of a patient with persistent, intractable pain at the gastrostomy site despite long-term opioid use. We attempted alcohol-based TAP neurolysis and rectus sheath neurolysis, which successfully provided pain control without further opioid usage.

The patient provided written consent for the publication of this case.

Case Report

A 70-year-old male patient visited our pain clinic in December 2017 with gastrostomy site pain that started after percutaneous radiological gastrostomy was performed in May 2017.

The patient did not have any previous medical history, except for esophageal cancer located 26–32 cm inferior to the upper incisors. He received concurrent chemotherapy for a month in January 2017 but exhibited worsening of dysphagia and a consequent tendency of aspiration. For proper feeding, he underwent percutaneous radiological gastrostomy in May 2017.

Although he experienced constant pain near the gastrostomy site immediately after the procedure, oncologist continued the use of the percutaneous endoscopic gastrostomy (PEG) tube due to the persistent tendency of aspiration. In June 2017, the patient was treated with a fentanyl patch 75 µg/h and short-acting fentanyl buccal Tab 400 µg for pain management and required hospitalization due to features of delirium suspected to originate from opioid treatment.

When he visited our pain clinic in December 2017, he was being fed via the PEG tube. There were no abnormal findings on the abdominal computed tomography images, and physical examination did not indicate infection of the gastrostomy site. The patient also underwent PEG tube exchange under image guidance to ensure proper positioning of the tube, prior to visiting our pain clinic.

The pain was localized to the gastrostomy site and nearby abdominal wall located left and inferior to the xiphoid process. In addition, the pain was dull, with no signs of tenderness or local inflammation (Fig. 1). The patient was given a combination of acetaminophen 325 mg and tramadol HCl 37.5 mg 4 times a day for pain management. Although the pain control was effective (numerical rating scale [NRS] score of 5/10) for ~2 h after drug intake, the patient sometimes experienced severe pain with an NRS score of 9/10.

In addition to the oral administration of acetaminophen and tramadol, we locally applied a lidocaine patch and lidocaine 2.5% and prilocaine 2.5% cream to the site, but this was not effective. The use of 10% lidocaine spray was effective for ~20 min after the use, and therefore was utilized together with other drugs.

Nevertheless, there was no persistent improvement in pain. In January 2018, we attempted left-sided subcostal TAP block using 0.8% mepivacaine 4 cm³, and triamcinolone 10 mg and additional local anesthetics infiltration at the gastrostomy site using 1% lidocaine 4 cm³, under ultrasonography guidance. Immediately after the procedure, the pain near the gastrostomy tube was alleviated by ≥ 50% but quickly became aggravated again. After 2 weeks, we performed additional left-sided subcostal TAP block and lidocaine local infiltration at the gastrostomy site. Previous procedures were repeated. However, substantial pain relief was unclear after the procedure, and we were forced to provide oral administration of acetaminophen 325 mg plus tramadol HCl 37.5 mg 3 times a day and short-acting oxycodone HCl 5 mg in case of severe pain. However, the pain control was not effective, and the patient visited the emergency center several times due to pain.

Subsequently, the patient’s dysphagia symptoms improved and the PEG tube was removed in May 2018. However, the patient continued to experience persistent abdominal wall pain near the...
This dull pain had an atypical tendency to worsen at night (NRS score of 9/10). As the pain relief from traditional medications (i.e., oxycodone HCl or acetaminophen 325 mg plus tramadol HCl 37.5 mg) was not effective, we considered additional opioid usage.

We explained to the patient that appropriate intake of the prescribed medication for pain control and dose titration are crucial. However, the patient strongly refused to use further opioid due to fear of using strong opioids—he reported a history of severe delirium caused by opioid usage (including high-dose fentanyl patch) prior to visiting our pain clinic, as well as side effects (i.e., constipation and drowsiness) after oral opioid usage after admission to our pain clinic. The patient continued to suffer from gastrostomy site pain and had difficulties in rehabilitation and daily activities (i.e., deep breathing and supraglottic swallowing) due to pain.

The effectiveness of oral medications, such as opioids, and of topical treatments, such as lidocaine patch, cream, and spray, was inappropriate. Whereas TAP block and local infiltration of lidocaine provided short-term pain relief by ≥ 50% without any side effects.

Therefore, we decided to perform left-sided TAP prognostic block and subsequent neurolytic block. We explained possible side effects (i.e., neuritis, deafferentation pain, or abdominal muscle weakness) and unclear long-term outcomes. The patient still wanted to undergo neurolytic TAP block.

We performed left-sided subcostal TAP using 0.5% bupivacaine 5 cm³ under ultrasonography guidance. The patient exhibited temporary pain relief (~5 h after procedure) and the pain worsened again, indicating positive outcome of prognostic block.

In June 2018 (7 days after), we performed left-sided subcostal TAP neurolysis. We identified the abdominal muscle layer and rectus sheath under ultrasonography guidance and injected 0.8% mepivacaine 3 cm³ using a 26-G spinal needle. We confirmed concordant pain relief after 5 min and injected 6 cm³ of 100% ethanol with the spinal needle (Fig. 2A). The total ethanol concentration for neurolysis was assumed to be 66%.

The patient did not experience any side effects except slight discomfort at the injection site immediately after alcohol injection and started to experience pain relief. The patient barely experienced any pain (NRS 0/10) immediately after neurolysis. On the outpatient visit 1 week later, he still experienced mild pain (NRS 3/10) near the medial tip of the gastrostomy site but had no pain in other sites. Pain relief was continuously observed until the 2-month outpatient follow-up, and we discontinued the use of opioids and utilized pregabalin 75 mg for abdominal pain control. However, 3 months after neurolysis, the patient started to experience abdominal pain at the medial tip of gastrostomy site (NRS 6/10), and we were forced to increase the pregabalin dose and use short-acting opioids such as oxycodone HCl.

The patient refused to use opioid again due to constipation and wanted other treatment option. We performed left-sided rectus sheath block using 0.5% bupivacaine 5 cm³ under ultrasonography guidance, and a positive outcome (pain relief) was observed.

On the 3rd month after the first neurolysis procedure, we performed rectus sheath neurolysis by injecting 0.8% mepivacaine 3 cm³ and then injecting 100% ethanol 7 cm³ (Fig. 2B). The total ethanol concentration for neurolysis was assumed to be 70%.

The patient did not experience discomfort during the procedure and started to experience pain relief. Pain at the medial tip of the gastrostomy site substantially reduced from NRS 6/10 to 2/10.

Fig. 2. (A) Transversus abdominis plane neurolysis ultrasonography image. EO: external oblique muscle, IO: internal oblique muscle. (B) Rectus sheath neurolysis ultrasonography image.

https://doi.org/10.4097/kja.19041
Currently, he is under 4-month follow-up, with pregabalin 150 mg 2 times a day and no opioid usage.

**Discussion**

Subcostal TAP block acts on the fascial plane between the internal oblique and transversus abdominis, which contain the nerves from T7 to T10, to establish sensory block of the abdominal wall. Rectus sheath block acts on the terminal branches of the 7–11th intercostal nerves, which penetrate the posterior wall of the rectus abdominis muscle. Therefore, it provides better coverage of sense organs near the midline of abdomen relative to TAP block [7]. Based on the location of the pain in different patients, an appropriate method should be utilized to ensure analgesia of the whole abdomen (Fig. 3).

Thus, depending on the location of the pain, rectus sheath neurolysis can be considered a treatment option for intractable pain management, along with TAP neurolysis.

TAP neurolysis cases reported thus far have been focused on pain management in patients with cancerous invasion of the abdominal wall. On the other hand, we report the case of a cancer patient who received intervention for the management of treatment-associated pain.

The patient in this case report suffered from atypical pain due to gastrostomy performed as a supportive part of cancer treatment, not because of abdominal wall invasion by the cancer.

Pain at the gastrostomy site often occurs acutely, and multiple causes including leakage, local infection, gastric mucosa irritation caused by tube malposition, peritoneum irritation, and pain caused by progression of the primary cancer have been reported [8].

For the patient in our case report, we assessed for potential malposition and local infection at the time of PEG tube exchange. However, the patient experienced persistent, atypical pain even after tube removal.

From the characteristics of the pain, we hypothesized that the patient was suffering from somatic and/or neuropathic pain of unknown etiology rather than from visceral pain. We attempted to provide pain relief using various medications including opioids and topical agents. However, despite the clear side effects of opioids, appropriate pain control was not achieved. More specifically, the patient was undergoing rehabilitation of supraglottic swallowing due to symptoms of dysphagia and aspiration tendency. The abdominal pain was hindering deep breathing.

Therefore, in order to prolong the effectiveness of TAP block using local anesthetics, we attempted neurolysis using alcohol, one of the agents used for peripheral nerve neurolysis, and successfully provided effective pain control and opioid sparing for ~4 months after the initial neurolysis.

In a previously reported case, TAP neurolysis using 33% ethanol was performed in a hospice patient with periumbilical pain due to abdominal wall mass associated with metastatic colon cancer, and although the pain decreased from NRS 7/10 to 0/10 over 2 days, the patient died on the 5th postoperative day because of cancer progression [5].

In another case series, TAP neurolysis using 33%–70% ethanol achieved pain reduction ≥ 50% over 17 days to 3 months in cases of abdominal pain due to colon cancer involving abdominal wall or neuroendocrine tumor involving abdominal wall [4].

A case report of TAP neurolysis using phenol for pain extending from the umbilicus to the pubis due to epithelioid sarcoma involving the abdominal wall reported pain reduction from NRS 5/10 to 0/10 over a maximum of 3 weeks [6].

The previously reported cases used neurolysis to relieve pain due to cancer directly involving the abdominal wall. Whereas in our case, we used neurolysis to treat pain of non-cancerous origin, and pain reduction was achieved for up to 4 months.

In this case report, we utilized alcohol as a neurolytic agent. For TAP neurolysis, there are reports of the use of either alcohol or phenol, but no previous study has compared the effectiveness of

![Fig. 3. Comparison of sensory block areas between left-sided subcostal transversus abdominis plane (TAP) block and bilateral rectus sheath block. Black oval: rectus sheath block, White oval: left subcostal TAP block.](https://doi.org/10.4097/kja.19041)
the two agents. A previous study that performed splanchnic nerve neurolysis for abdominal pain control has demonstrated that there is no difference in effect of phenol and alcohol [9], but additional studies are required for neurolysis of the abdominal wall.

As of now, the neurolytic agent should be selected considering multiple factors, including the following: painful stimulation at the time of alcohol injection, possibility of neuritis, and the surgeon’s convenience based on characteristics (i.e., viscosity of phenol).

In conclusion, although additional studies for the selection of the neurolytic agent and procedure indication/efficacy are needed, we demonstrated that alcohol-based TAP neurolysis and rectus sheath neurolysis provide effective pain control and opioid sparing in a cancer patient with chronic treatment-related pain involving the abdominal wall.

Conflicts of Interest

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

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https://doi.org/10.4097/kja.19041
Seroconversion of red blood cell antibody in ABO-incompatible living donor liver transplantation
-a case report-

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Background: Liver transplantation usually requires blood transfusion, and a red blood cell (RBC) antibody screen is essential for the prevention of a hemolytic reaction. Since proper ABO-compatible grafts are lacking, ABO-incompatible living donor liver transplantation (ABO-i LDLT) with desensitization is a feasible therapy. Desensitization includes intravenous rituximab injection and plasmapheresis before surgery. Case: A 60-year-old female was diagnosed with hepatitis B virus-related hepatocellular carcinoma and planned for ABO-i LDLT. She tested positive in a RBC antibody screen over two years; however, she tested negative for the test after desensitization. Clinicians noted the seroconversion during induction, and thus, a delay in the preparation of adequate packed RBC was unavoidable. Conclusions: Even when the latest RBC antibody screen is negative after immunosuppression, clinicians should consider the possibility of a prior positive result to promote safer medical treatment and management.

Keywords: Erythrocytes; Liver transplantation; Plasmapheresis; Red blood cell antibody screen test; Rituximab.

Patients with chronic liver disease often have impaired coagulation and thrombocytopenia. They also have hyperdynamic circulation and the liver is well-known for receiving approximately a quarter of cardiac output. Liver transplantation (LT) is the treatment of choice for patients with end-stage liver disease. There is a risk of massive bleeding during LT and transfusion is frequently required. ABO typing and a red blood cell (RBC) antibody screen help to find safe blood and prevent a hemolytic transfusion reaction during allogeneic transfusion. ABO typing is also important for donor selection to prevent graft rejection. Since there are shortage with ABO-compatible graft, ABO-incompatible graft is a potential solution with comparable results [1,2].

Although there is no definite protocol for ABO-incompatible living donor liver transplantation (ABO-i LDLT), the recipient is usually treated with the anti-CD20 monoclonal antibody, rituximab and plasmapheresis before LT [1–3]. Rituximab suppresses B lymphocytes similar to that in a chemical splenectomy. Plasmapheresis removes antibodies in the plasma by exchanging fluid. These preparations are aimed to reduce antibodies against the incompatible ABO blood type antigens of the graft and to increase graft survival. Here we report a case of RBC antibody screen conversion before ABO-i LDLT.
Case Report

A 60-year-old female patient (height: 157 cm, body weight: 45.9 kg) was diagnosed with hepatitis B virus-induced liver cirrhosis and hepatocellular carcinoma (HCC) six years ago. She had been treated five times with trans-arterial chemoembolization and palliative radiotherapy. She used an albuterol inhaler once a month for asthma but never visited the emergency department with exacerbation. Two and four years prior to presentation, she had an umbilical hernia repair and total thyroidectomy for papillary thyroid carcinoma, respectively. She was taking an antiviral agent for hepatitis B virus, warfarin for portal vein thrombosis, and diuretics for ascites. Despite the hospitalization and medication, ascites was refractory and laboratory values had improved slightly. As her liver cirrhosis progressed, and HCC was unresectable, LT was planned. Preoperative hematocrit was 0.283% (normal range: 0.318–0.438%), hemoglobin was 9.2 g/dl (normal range: 11.2–14.8 g/dl), platelet count was 63000 /μl (normal range: 138000–347000 /μl), prothrombin time with an international normalized ratio was 1.17 (normal range: 0.90–1.10), sodium was 133 mmol/L (normal range: 135–145 mmol/L), and the model for end-stage liver disease score was 15 points. Vital signs were within the normal range. Preoperative chest radiography confirmed no active lung lesion, but the diaphragm was elevated toward the left side. The pulmonary function test showed a combined severe obstructive and moderate restrictive pattern. Transthoracic echocardiography showed diastolic dysfunction grade 1. The esophagastroduodenoscopy revealed esophageal varices, portal hypertensive gastropathy, and gastric varices at cardia. One of her sons was willing to donate his liver, however, his blood type was AB while the patient’s was A. For immunosuppression, she received a single intravenous dose of rituximab (525 mg; 375 mg/m² body surface area) two weeks prior to LT. Isoagglutinin immunoglobulin M (IgM) and G (IgG) titers against B antigen were measured before the rituximab injection and every morning for 7 days before the surgery, using a standard direct-agglutination technique (Fig. 1). Our hospital protocol is based on the American Society for Apheresis and the American Association of Blood Banks 2016 guidelines for apheresis [4]. Target isoagglutinin titer was less than 1 : 16, and 13 units of AB type fresh frozen plasma (FFP) as 1 estimated plasma volume (EPV) were used for each plasmapheresis (2 h). Target isoagglutinin titer was achieved by two consecutive plasmaphereses and LT was scheduled for the next day after two more plasmaphereses. The latest RBC antibody screen 1 day prior to operation was negative so it did not draw the clinicians’ attention. In the operation theater, electrocardiography, pulse oximetry, and non-invasive blood pressure were conducted. Two puffs of albuterol were administered. We asked the blood bank to prepare 5 units of packed RBCs of blood group A, considering the patient’s medical history, operation history, and laboratory evaluations. Anesthesia

![Figure 1](https://doi.org/10.4097/kja.19141)
was induced with thiopental sodium (250 mg), rocuronium (50 mg), and 5 volume% of sevoflurane following preoxygenation for 3 min. After intubation, radial artery cannulation was performed on the right side with a 20 gauge (G) catheter and bispectral index (BIS, Medtronic, USA) monitoring started. However, the hospital blood bank informed us that her RBC antibody screen test had been positive 2 days prior to surgery. We reviewed her medical record thoroughly and found that a pack of single-donor platelets (SDP) had been transfused twice, 3 and 2 years prior to presentation. Prior to the first transfusion, she was negative for RBC antibody screen. However, prior to the second transfusion, she was positive for the antibody screen and both anti-C (Rh system) and anti-M (MNS system) were identified [5]. The blood bank also noticed that there was only one unit of matched packed RBCs. The induction was postponed for 3 h until four more units of packed RBCs from other blood banks were received and cross-matched. Two 20 G catheters (SAC-00820 20 G 8 cm, Arrow International, USA) were inserted in the right femoral artery and vein. A 7 French central catheter (REF CS-15703-E 7 Fr 3 lumen 20 cm, Arrow International, USA) was placed through the left internal jugular vein under ultrasound guidance. She already had an 8.5 French permanent catheter inserted through the right internal jugular vein as a route for plasmapheresis. The magnetic induction fluid warmer (Belmont Instrument, Fluid Management system 2000, USA) was connected and the FloTrac/Vigileo system (Edwards Lifesciences, USA) monitoring started. Due to the stricture in the inferior vena cava (IVC), the surgeon performed IVC reconstruction and re-perfused three times. Methylprednisolone (500 mg) was infused during portal vein anastomosis and basiliximab (20 mg) was infused after reperfusion for immunosuppression.

After the bleeding around the hepatic artery was controlled, the diaphragm was repaired, and two chest tubes were inserted. The patient was transferred to the surgical intensive care unit with an open abdomen. The total anesthesia time was 16 h and 30 min and the patient received approximately 17,500 ml of crystalloid, 1,200 ml of 5% albumin, 1,500 ml of 6% hydroxyethyl starch (VoluLyte, Fresenius Kabi, Germany), 5 units of pre-storage leukocyte-reduced RBCs, 5 units of leukocyte-depleted RBCs, 4,872 ml of Cell Saver (Haemonetics, USA) blood, 9 units of blood type AB FFP, 2 units of blood type AB SDP, and 12 units of blood type AB cryo-precipitate. Intraoperative blood loss expressed with lost red cell mass was 4,123 ml [6] and urine output was 1,320 ml. The wound was closed in the operation theater on postoperative day (POD) 2 and wedge biopsy of the transplanted liver was also conducted. The biopsy revealed centrilobular hemorrhagic necrosis of hepatocytes, implying outflow impairment. The graft was not functioning well with stricture of the hepatic vein. As mechanical ventilation was prolonged, tracheostomy was applied on POD 7. Both IgM and IgG antibodies gradually increased but stayed under the target range (1 : 4 and 1 : 8, respectively) (Fig. 1). No further plasmapheresis was performed as the low level of IgM titer was maintained. Re-transplantation had been planned while the patient waited in the intensive care unit; however, she expired due to sepsis on POD 31.

Written informed consent for publication could not be obtained from the deceased patient.

Discussion

There are 346 RBC antigens and 308 of them are assigned to 36 blood group systems. These blood group systems can be classified based on carbohydrates, glycoporphins, complement regulation, adhesion and receptor molecules, transporters and channels, and enzymes [7]. Generally, blood typing for the ABO and D antigens and RBC antibody screen are performed before major surgery. The RBC antibody screen is known as an antibody screen test. It can be performed manually or by automation and by mixing the recipient’s plasma and two or three collections of clinically significant RBC antigens. If the screen shows any agglutination, it is considered positive, and an antibody identification test is required to detect the specific antibody responsible. The compatibility test or cross-matching is required before RBC transfusion. Matching only for blood typing has a 99.8% chance of compatible transfusion. The possibility can be increased to 99.95% with RBC antibody screen and cross-matching [8]. Unlike the ABO antibody, other RBC antibodies are rarely produced spontaneously, and such antibodies are called unexpected antibodies. In this case, the patient developed the RBC antibody after platelet transfusion without pregnancy or RBC transfusion. Platelets express a few RBC antigens that rarely generate antibodies, and there can be residuals or fragments of RBCs remaining in the platelet concentrates [5,9].

There was only a 3% chance of having proper packed RBCs since the frequency of C-negative and M-negative phenotypes in the Korean population are about 13% and 25%, respectively [10]. As liver transplantation (LT) usually requires blood transfusion, we routinely prepare intraoperative cell salvage to reduce allogenic transfusion. Autotransfusion can reduce immunologic events and contains 2,3-diphosphoglycerate (2,3-DPG). In stored RBCs, 2,3-DPG levels are decreased, and the oxyhemoglobin dissociation curve shifts left. Nevertheless, time is required until sufficient blood can be collected. In this case, because of the patient’s cancer, the blood needed to be filtered to remove possible cancer cells [11].

https://doi.org/10.4097/kja.19141
As the use of ABO-incompatible organs is increasing, immunosuppressive therapy is important to prevent both hyperacute rejection and acute antibody-mediated rejection (AMR) [1,2]. B lymphocytes produce antibodies including RBC antibodies, so their suppression during ABO-incompatible organ transplantation is imperative. Rituximab targets the CD20 antigen on the surface of B lymphocytes and depletes them. Morimoto et al. [12] found B lymphocytes were not detectable after two weeks of rituximab injection and the effect lasts for several months [12] and that rituximab injection earlier than 7 days before transplantation significantly reduced the frequency of AMR in ABO-i LDLT [13]. Standardizing the time of administration and the dosage adjustment still require further investigation [1,2,13].

Perioperative plasmapheresis reduces anti-A or anti-B antibody titers and improves graft survival in ABO-incompatible organ transplantation. There is no standard recommendation for target antibody titer. A titer of 1:64 or above would increase the risk of AMR and complications of transplantation. Plasmapheresis can be performed with FFP, albumin, or crystalloids. Volume exchange with 1 EPV removes 63% of antibodies, while 1.4 EPV removes 75%. For most cases, a volume of 1–1.4 EPV is exchanged [4]. In our case, levels of IgM and IgG against B antigen titers were reduced or equal a day after plasmapheresis (Fig. 1). Levels of IgM against B antigen doubled 2 days after the second plasmapheresis. After plasmapheresis, intravascular re-equilibration and re-synthesis can increase antibody titer [14]. After the third plasmapheresis, the RBC antibody screen converted from positive to negative. There was no agglutination with the machine and the laboratory performed another manual RBC antibody screen, but it was still negative. Although plasmapheresis aims to remove a specific antibody, large molecular-weight substances including other antibodies, complement components, and albumin can be removed [15]. In our case, serial plasmapheresis might have removed not only antibodies against B antigen but also anti-M and anti-C. As the number of antibodies is reduced by plasmapheresis, the concentration is also reduced by dilution. Rituximab has a role in sustained undetected RBC antibody screens by depleting memory B lymphocytes. Antibodies cannot be adequately replenished by the depleted B lymphocytes.

In our electronic medical record system, if a patient is positive for an RBC antibody screen once, the patient is always marked with ‘Ab’ in the patient information window. On the other hand, the RBC antibody screen result window displays only for the specific test. We overlooked the patient information window and only focused on the latest result window because the RBC antibody screen rarely changes from positive to negative. A system revision for the RBC antibody screen result window will improve patient management and safety. In conclusion, meticulous concern on the serial results of RBC antibody screens is necessary after immunosuppression, before ABO-incompatible solid organ transplantation.

Conflicts of Interest

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

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https://doi.org/10.4097/kja.19141
Flail arm syndrome (FAS), also known as ‘man-in-the-barrel’ syndrome or brachial amyotrophic diplegia, is an atypical presentation of amyotrophic lateral sclerosis (ALS). It is differentiated from ALS by lower motor neuron type proximal muscle weakness of only the upper limbs. The lower limbs may show mild upper motor neuron type weakness, but the bulbar and respiratory muscles are not affected. It has a progressive course with a male-to-female ratio of 4 : 1 [1]. FAS is one of the spectra of motor neuron disease (MND) and shares many of the pathophysiological features of MND. MND is a degenerative disease of the spinal cord tracts and leads to respiratory muscle atrophy due to the ongoing, chronic process of denervation and re-innervation of muscles.

We describe the anesthetic management of a 50-year-old male (164 cm tall and 54 kg) that had FAS with bilateral proximal upper limb weakness and chronic obstructive respiratory disease. The patient was a chronic smoker. He had been recently diagnosed with an epigastric hernia and was scheduled for a mesh hernioplasty. The patient had gradual and symmetrical weakness of his proximal muscles of both upper limbs, for 2 years, with no wasting or weakness in the distal muscles. His symptoms had worsened over the previous 6 months. There was severe wasting of the bilateral shoulder and arm muscles, with the power grading being 2/5. The patient's neurophysiological assessment was normal. A muscle biopsy suggested neurogenic atrophy. Pulmonary function assessment indicated moderate obstruction on spirometry. The patient was at risk of acute respiratory failure due to his respiratory status and the general aspiration risk of MND patients. Hence, we decided to adopt a transverse abdominis plane (TAP) block as our first choice of anesthesia. If the block failed, we were prepared to administer total intravenous anesthesia (TIVA) with propofol and dexmedetomidine without a muscle relaxant. Bronchodilator nebulization and anti-aspiration prophylaxis were done in the preoperative preparation. Under all aseptic precautions, the patient was given an ultrasound-guided bilateral subcostal TAP block, using 15 ml of 0.5% ropivacaine on either side. The patient was also given mild sedation with dexmedetomidine bolus of 50 μg over 10 minutes, followed by 25 μg/h. The total duration of the procedure was ninety minutes. Intra-operative management was uneventful, and the patient was shifted to the postoperative anesthesia unit with stable hemodynamics and respiratory status. There were no adverse effects on the patient’s vitals, respiratory depression, sedation, and muscle weakness observed during the postoperative period.

There is a lack of literature in the anesthetic management of patients with FAS. In FAS patients, we have the same anesthetic considerations as those with ALS or MND. Neuromuscular monitoring and the need for postoperative mechanical ventilation must be anticipated where muscle relaxants cannot be avoided [2]. Depolarizing muscle relaxants such as succinylcholine are not recommended because of reported rhabdomyolysis and...
hyperkalemia from denervated muscles, possibly leading to ventricular arrhythmias and fibrillation. Their use in patients with ALS has also been associated with neuro-myotonia. Inhalational agents are known to potentiate a neuromuscular blockade as they possess intrinsic neuromuscular blockade activity. Regional anesthesia is preferred in patients with MND to avoid aspiration and the possibility of a prolonged neuromuscular blockade following general anesthesia. However, the use of a central neuraxial blockade may also exacerbate the progression of the disease course. Demyelination of the nerve fibers makes the patients more susceptible to the neurotoxic effects of local anesthesia [3]. Therefore, the preferred anesthetic technique in these patients is TIVA or regional anesthesia. Thampi et al. [4] described the use of TIVA with an obturator nerve block in the successful anesthetic management of a patient with ALS for transurethral resection of the prostate. The TAP block targets the myocutaneous nerves to the anterior abdominal wall (T6 to L1). The subcostal approach blocks the sensory nerves from T6 to T10, which is sufficient for surgeries with an incision above the umbilicus. The major advantages that a subcostal TAP block offers over general anesthesia include a lower opioid requirement, decreased incidence of postoperative respiratory depression, nausea, and vomiting. As compared to central neuraxial blocks, the advantages include the absence of a sympathetic block and avoidance of disease progression. The primary challenge in the anesthetic management of patients with FAS is to guarantee optimal surgical conditions while preserving the perioperative neuromuscular and respiratory function of the patient close to the pre-operative baseline status. Mild sedation and a bilateral subcostal TAP block ensured adequate anesthesia, analgesia, and immobility. Besides, we were able to efficiently manage the case while avoiding the aggravation of neuromuscular weakness and aspiration. To the best of our knowledge, this is the first safe use of dexmedetomidine along with a TAP block in an MND case.

Acknowledgements

We would like to acknowledge Dr. Farhanhul Huda and his surgical team, for excellent surgical skills, meticulous approach and dedication towards patient’s care.

Conflicts of Interest

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

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References

Medication shortages are an ongoing obstacle for clinicians in the United States [1]. The American Society of Health-System Pharmacists has established guidelines on managing drug product shortages and recommends healthcare worker education to mitigate and prevent drug shortages [1]. In the face of drug shortages, inventory control personnel and multidisciplinary healthcare teams should consider therapeutic equivalents and alternatives to critical medications to avoid inadvertent harm to or inferior treatment for patients [1,2].

The role of ketamine in Enhanced Recovery Protocols (ERP) has been well described in the literature [3]. There is evidence that ketamine helps to attenuate central sensitization and hyperalgesia, thus reducing opioid tolerance [4] and making it effective in reducing postoperative pain. To minimize opioid use, surgeons and anesthesiologists aim to provide multimodal analgesia through parenteral and enteral pharmacologic adjuncts and alternatives to opioids. The purpose of this study was to evaluate the intravenous ketamine waste associated with two different ketamine dosage preparation methods.

The project was approved by the Quality and Safety Committee (#869) at the University of Pittsburgh Medical Center. This is a retrospective analysis of the wasted drug amounts of ketamine for patients undergoing complex abdominal surgery (such as colec- tomy, pancreas resection, liver resection, or laparotomy) via an ERP from January 2017 to March 2018 at a single university medical center. Patients were excluded if the patient had more than one surgery within 24 h, did not receive intraoperative ketamine, or received a formulation of ketamine intraoperatively that deviated from the standard medication supply with concentration of 10 mg/ml for induction and 2 mg/ml for infusion.

Retrospective chart review was used to gather data on bolus dose upon induction of anesthesia (0.75 mg/kg), infusion dose (0.4 mg/kg/h), and total intraoperative dose of ketamine. Standard ketamine concentration supplied for all induction doses were 200 mg/20 ml vials (10 mg/ml), of which the calculated dose was administered while the remaining amount was wasted. Standard ketamine concentration supplied for maintenance intraoperative infusion was 200 mg in 100 ml (2 mg/ml) normal saline solution (NSS). Based on the standard ketamine formulations supplied and the actual patient consumption, drug waste was calculated. Data are presented as mean ± SD.

During the 14 month period, 988 surgeries utilizing ERPs occurred, of which 318 were excluded. For the remaining 670 surgeries done with ERPs, a total of 95,140 mg of intraoperative ketamine was consumed during the induction and maintenance infusions for all 670 patients (Table 1). The mean bolus dose on induction, taken from a 200 mg vial of ketamine, was 46 ± 18 mg. The mean intraoperative infusion total dose administered from a 200 mg in 100 ml NSS bag of ketamine was 96 ± 58 mg.
Medication waste was estimated to total 178,551 mg (266 mg/patient). Induction dose waste alone was estimated to exceed 101,582 mg of ketamine or 153 mg ± 18 mg per patient. Infusion waste was estimated to exceed 76,969 mg or 115 mg ± 48 mg per patient.

After identifying an alternative suited our institutional needs, ketamine 100 mg in 10 ml (10 mg/ml) syringes were procured to be utilized for both induction and maintenance intraoperative infusion. The medication waste was estimated to be 268 mg/patient but decreased the mean total ketamine consumption to 106 mg/patient. The mean ketamine waste avoidance per patient was calculated as 162 mg/patient, resulting in 108,540 mg of potential ketamine waste avoidance in our patient cohort of 670 patients. This is a 61% reduction in waste when compared to the estimated medication waste of 178,551 mg, resulting in an estimated cost savings of $7,046.

Based on the results of this analysis, our institution standardized dispensing practices to include 100 mg of ketamine hydrochloride in 10 ml (10 mg/ml) for induction bolus and maintenance infusion with an electronic syringe smart pump. Amidst the national shortage, we identified two 503B compounders to supply us with ketamine in the form of a 100 mg (10 mg/ml) syringe. 503B compounders are drug compounding facilities established by the federal Drug Quality and Security Act in the United States. These facilities prepare personalized compounded medications for patients and for use by physicians. When pre-filled ketamine syringes are not available, ketamine is compounded pursuant to patient specific order under sterile conditions in our operating room satellite pharmacy’s Contained Aseptic Isolator.

The surgical protocol at our university hospital includes an induction dose of 0.75 mg/kg followed by an infusion ranging between 0.4 and 0.6 mg/kg depending on the type of ERPs ordered [5]. There is also an agreement among our experts that low dose or sub-anesthetic doses of ketamine, when added as an adjunct to general anesthesia reduces postoperative pain and opioid requirements [4]. Opioid sparing effects of ketamine may be masked when the drug is used in small doses (0.15 mg/kg) against the background of multimodal or epidural analgesia [5]. It is known that nociceptive and inflammatory signals are generated throughout surgery and after the procedure, to prevent pathologic pain, in an attempt to reduce sensitization of central and peripheral pain pathways [5]. Ketamine administration can also lead to a longer time spent in the post anesthesia care unit, longer time to patient discharge secondary to less controlled pain, and increased opioid requirements.

The primary limitation of the study was that potential medication waste avoidance was calculated and did not consider actual medication savings as we utilized a retrospective comparative analysis method that did not include patients who received the alternative preparation of ketamine. Lastly, we only predicted the amount of ketamine saved using the current institutional supplier, due to the use of our 503B compounder and the intermittent availability of ketamine syringes nationally.

Clinicians continue to experience supply challenges for numerous medications. We conclude that the utilization of alternative concentration ketamine 10 mg/ml 10 ml syringes could reduce both overall and average ketamine waste per case. Our study shows that a multidisciplinary approach to analyze institutional best practices assisted in the standardization of shortage mitigation approaches related to ketamine without restricting patient access to this drug.

Table 1. Ketamine Waste Analysis

<table>
<thead>
<tr>
<th></th>
<th>Former state</th>
<th>Current state</th>
<th>Difference between former and current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intraoperative dose per patient (mg)*</td>
<td>142</td>
<td>142</td>
<td>0</td>
</tr>
<tr>
<td>Induction, mean dose</td>
<td>46 ± 18</td>
<td>45 ± 18</td>
<td>1 ± 18</td>
</tr>
<tr>
<td>Infusion, mean dose</td>
<td>96 ± 58</td>
<td>95 ± 58</td>
<td>1 ± 58</td>
</tr>
<tr>
<td>Induction, mean waste</td>
<td>153 ± 18</td>
<td>152 ± 18</td>
<td>1 ± 18</td>
</tr>
<tr>
<td>Infusion, mean waste</td>
<td>115 ± 48</td>
<td>114 ± 48</td>
<td>1 ± 48</td>
</tr>
<tr>
<td>Total ketamine induction waste</td>
<td>101,582 (508 vials)</td>
<td>36,642 (184 vials)</td>
<td>64,940 (324 vials)</td>
</tr>
<tr>
<td>Total ketamine infusion waste</td>
<td>76,969 (385 vials)</td>
<td>34,269 (172 vials)</td>
<td>42,690 (213 vials)</td>
</tr>
<tr>
<td>Total ketamine waste†</td>
<td>178,551 (893 vials)</td>
<td>70,911 (356 vials)</td>
<td>107,640 (537 vials)</td>
</tr>
<tr>
<td>Total cost waste</td>
<td>$11,609</td>
<td>$4,628</td>
<td>$7,046</td>
</tr>
</tbody>
</table>

*Total intraoperative dose includes bolus dose upon induction of anesthesia (0.75 mg/kg), infusion dose (0.4 mg/kg/h), and total intraoperative dose of ketamine. †The standard ketamine formulations supplied and the actual patient consumption.
Conflicts of Interest

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

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https://doi.org/10.4097/kja.20049
We read with great interest an article by Lim and Wong [1] describing supraglottic airway guided flexible bronchoscopic intubation (SAGFBI). We congratulate them for highlighting that this method can be very useful in certain circumstances. In this regard, we wish to add our experience of this technique as we practice it regularly. Informed written consent has been obtained for presentation and publication of cases from the patients.

The most important suggestion, we wish to make regarding this method is that at our institute we allow the patient to gently introduce the supraglottic device himself/herself (Fig. 1). We believe that it is better than allowing an anesthesiologist to place the device in the oropharynx of an awake patient. Often, we notice that oral anesthesia is not adequate and the gag reflex persists despite trying various methods. A person introducing the device themself does so making subtle adjustments to suit his/her comfort, at his/her own pace. This decreases his/her anxiety associated with the procedure and enhances cooperation, which is crucial for an awake procedure. Moreover, it results in lesser trauma, coughing, and gagging. We place the person at a 45 degree head up position and the anesthesiologist stands behind to provide assistance and keep an eye on the placement. For troubleshooting in such cases, an alternate lateral approach by the side of the mouth is required sometimes. Assisted by an anesthesiologist, the patient can himself/herself, again manipulate the device in a gentler and less traumatic manner.

The choice of device also has a bearing on success of the technique. The authors have described advantages of Ambu AuraGain™ (Ambu®, Denmark) versus ProSeal™ laryngeal mask airway (PLMA) (Teleflex®, USA). We feel that a preformed second-generation device with an inflatable cuff is a good choice. Devices such as Intubating LMA or PLMA which have metallic introducers [2], may not be suitable for awake placement due to the hard non-malleable metal. Doctors have attempted to use i-gel® (Intersurgical Ltd., UK) in an awake patient for difficult airway management [3]. A previous study described successful use of i-gel® as a conduit for intubation using a fiberscope in sedated patients. However, there has been no comparison of devices and even in this study, patients were not fully awake [4]. We have noted that i-gel® is not very comfortable for awake placement. It has a wide and hard shaft with a non-inflatable cuff [5]. The gag elicited from this device is stronger than many other supraglottic devices though no trials have been performed comparing any device for awake placement. To reduce the gag reflex associated with awake placement of such devices, we encourage patients to gargle with lignocaine for as long as they can. We subsequently ask them to gently swallow it all. We believe this allows for better anesthesia of the oropharynx and also a part of the upper esophageal sphincter region. We feel that by taking the above mentioned measures into account, we can ensure better patient management when practicing SAGFBI.
Conflicts of Interest

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

Author Contributions

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References


The tricuspid valve (TV) has been long been referred to as the ‘forgotten valve,’ though recently, understanding of the long-term consequences of untreated tricuspid pathology has improved. The 2014 American Heart Association/American College of Cardiology guidelines for the Management of Patients with Valvular Heart Disease list Class I evidence for TV repair/replacement in patients with severe tricuspid regurgitation (TR) or stenosis undergoing left-sided valve surgery [1].

However, bioprosthetic valves undergo degeneration over time. Re-operative surgical valve replacement is the standard of care but can be associated with significant operative mortality and morbidity, ranging from 13% to 37% [2].

Transcatheter tricuspid valve-in-valve (TVIV) implantation has emerged as an attractive alternative to surgical valve replacement in bioprosthetic valve dysfunction in patients at prohibitive surgical risk.

We present a patient who successfully underwent transcatheter TVIV implantation as a salvage treatment option for bioprosthetic failure. Written consent was obtained. A 38-year-old male was admitted with symptoms of significant scrotal edema causing severe pain and impairing ambulation, shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, and ascites. Past medical history included human immunodeficiency virus infection on highly active antiretroviral therapy, hypertension, pulmonary artery pseudoaneurysms, and substance abuse complicated by multimicrobial TV endocarditis. He had undergone two previous open TV surgeries (one for repair, one for replacement) with poor recovery following sternotomy, bioprosthetic valve endocarditis subsequently treated, and septic pulmonary emboli. He was diagnosed with severe bioprosthetic TV regurgitation and co-existing TV stenosis. A pre-operative transesophageal echocardiogram (TEE) revealed a TV mean pressure gradient of 17 mmHg and no evidence of vegetations on the valve. Due to his comorbidities and past surgical history, he was deemed a prohibitive-risk surgical candidate. After multidisciplinary discussion, a decision was made to perform a transfemoral transcatheter TVIV replacement.

After placement of a pre-induction arterial line, general anesthesia (GA) was induced and a central venous catheter and TEE probe placed post-induction. Pre-procedural TEE revealed severe TR and stenosis, with mean pressure gradient of 17 mmHg and no evidence of vegetations on the valve. The tricuspid valve (TV) has been long been referred to as the ‘forgotten valve,’ though recently, understanding of the long-term consequences of untreated tricuspid pathology has improved.

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After placement of a pre-induction arterial line, general anesthesia (GA) was induced and a central venous catheter and TEE probe placed post-induction. Pre-procedural TEE revealed severe TR and stenosis, with mean pressure gradient of 17 mmHg. Femoral artery access was secured by the surgical team to facilitate emergent cardiopulmonary bypass, if needed. A Swan-Ganz catheter inserted from the femoral vein into the right ventricle (RV), was exchanged in a series of steps and a 29-mm Edwards Sapien 3 valve successfully deployed (Fig. 1) within the bioprosthetic TV. Hemodynamic stability improved
immediately. TEE showed significant reduction in the TV mean pressure gradient from 14 to 1 mmHg with no residual TR. The procedure was well tolerated, and the patient extubated in the operating room with no adverse postoperative events.

While 300 cases have been reported over the last decade, TVIV is still uncommon. Successful anesthetic management requires assessment and optimization of comorbidities common in these patients, such as right heart failure, liver and renal dysfunction, and debilitation. It is also important to understand procedure-related special considerations.

Although it is feasible to perform these procedures under sedation, GA is preferred when intraoperative TEE is used. Invasive monitoring consists of arterial line and central venous catheter insertion due to potential for hemodynamic instability and necessity for vasopressor administration. Anticoagulation is typically achieved with 100 units/kg of heparin to achieve an activated clotting time of > 250 s, after vascular access is obtained by the surgeons [3]. Since there is a risk of a right ventricular pacing lead being jailed between the two prostheses or damaged, pacing during valve deployment may be induced by an electrode placed in the right atrium, coronary sinus, or left ventricle. The valve may also be deployed without pacing—as in our patient—due to the low flow velocity in the right ventricular outflow tract, as compared to the left side. Adenosine has also been used during valve deployment. These patients are usually extubated at the end of the case.

Several major anatomical challenges exist in transcatheter TV therapy as compared to other valves [4]. The tricuspid annulus is large, non-planar, and elliptical in shape. This, coupled with the angulation of the tricuspid annulus relative to the superior and inferior vena cava, can preclude optimal alignment of the delivery system. The annulus is proximal to many critical structures—the right coronary artery, coronary sinus, atrioventricular node, and Bundle of His—which may be damaged during deployment. Trabeculations and muscle bands within the RV can impede device positioning and equipment retrieval. Preoperative echocardiography is important not only to assess the severity and etiology of bioprosthetic valve failure but also to identify contraindications such as endocarditis. Evaluation of prosthesis size is important and determined via an integrated approach informed by the manufacturer’s reported internal diameter, mean diameter as measured by computed tomography, three-dimensional (3D) TEE, and fluoroscopy [5]. The angulation of the valve annulus in relation to the access route is also assessed.

Intraoperatively visualization is provided by 2D and 3D TEE and fluoroscopy. TEE can confirm transcatheter valve position before deployment, assess for post-implantation complications, and evaluate function. Functional evaluation includes confirmation of correct position, annular stability, leaflet mobility, assessment of pressure gradients and valve area, as well as presence and severity of any intravalvular or paravalvular regurgitation. TEE provides early detection of malposition, embolization events, and pericardial effusion.

To conclude, rapidly evolving advancements in the percutaneous treatment of structural heart disease coupled with improved understanding of the long-term consequences of untreated tricuspid pathology have led to the emergence of transcatheter TV replacement as a promising option for management of high-risk patients with failed surgical bioprostheses. It is important for the anesthesiologist to understand the special considerations involved with transcatheter TVIV.

**Conflicts of Interest**

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

**Author Contributions**

Seema P. Deshpande (Conceptualization; Writing – original draft; Writing – review & editing)
Susan Sankova (Writing – original draft; Writing – review & editing)
Nicolas Dorsey (Writing – original draft; Writing – review & editing)
Murtaza Y. Dawood (Writing – original draft; Writing – review & editing)
Kenichi Tanaka (Writing – original draft)

https://doi.org/10.4097/kja.20104
Deshpande et al. · Transcatheter tricuspid valve-in-valve

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References

An ultrasound-guided fascia iliaca catheter technique does not impair ambulatory ability within a clinical pathway for total hip arthroplasty

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Departments of Anesthesiology, Perioperative and Pain Medicine, Orthopaedic Surgery, Stanford University School of Medicine, Stanford, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA


The article by Mudumbai SC, et al. entitled, “An ultrasound-guided fascia iliaca catheter technique does not impair ambulatory ability within a clinical pathway for total hip arthroplasty” contained an error in the result.

Before correction:
Page 371, The primary outcome, total ambulation distance in meters (median [Q1-Q3]), did not differ between the two groups (FIC 63 [30–120] vs. ITM (83 [48–114]; P = 0.08).

The correct information is found below:
Page 371, The primary outcome, total ambulation distance in meters (median [Q1-Q3]), did not differ between the two groups (FIC 63 [30–120] vs. ITM (83 [48–114]; P = 0.08).

The authors apologize for any inconvenience this mistake may have caused.

Before correction:

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

(Equation 12)

The correct information is found below:

\[
\text{Adjusted sample size} = \frac{\text{Calculated sample size}}{1 - \text{dropout rate}} = \frac{39}{1 - 0.1} = 43.33
\]

(Equation 12)

The value for dropout rate was incorrectly printed as 0.9. The value for dropout rate should be corrected to 0.1.

The authors apologize for any inconvenience this mistake may have caused.
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For the policies on research and publication ethics that are not stated in these instructions, the Good Publication Practice Guidelines for Medical Journals, available at: www.kamje.or.kr/intro.php?body=publishing_ethics, or the Guidelines on Good Publication, available at: publicationethics.org/, can be applied.

1. Conflict-of-interest statement
Conflict of interest exists when an author or the author’s institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having a great potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and the background of the completed research.

2. Statement of informed consent and Institutional Review Board approval
If the study in the article is on human subjects or human-originated material, informed consent for the study and the IRB approval number needs to be provided. Copies of written informed consents and Institutional Review Board (IRB) approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to make potential ethical issues clear.

3. Statement of human and animal right
Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2018) (available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. Human subjects should not be identifiable, such that patients' names, initials, hospital numbers, dates of birth, or other pro-
4. Registration of the clinical trial research
Any researches 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/).

5. Reporting guidelines
The KJA recommends a submitted manuscript to follow reporting guidelines appropriate for various study types. Good sources for reporting guidelines are the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network (www.equator-network.org/) and the U.S. National Library of Medicine's (NLM's) Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html).

6. Authorship
Authorship credit should be based on: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; AND 2) drafting the article or revising it critically for important intellectual content; AND 3) final approval of the version to be published; AND 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these 4 conditions. If the number of authors is equal to or greater than 2, there should be a list of each author’s role in the submitted paper. Authors are obliged to participate in peer review process. All others who contributed to the work who are not authors should be named in the Acknowledgements section. KJA has a strict policy on changes to authorship after acceptance of the article and will only consider changes in the most extraordinary situations once the article is accepted.

7. Plagiarism and duplicate publication
Plagiarism is the use of previously published material without attribution. The KJA editorial office screens all submitted manuscripts for plagiarism, using a sophisticated software program, prior to peer review. When plagiarism is detected at any time before publication, the KJA editorial office will take appropriate action as directed by the standards set forth by the Committee on Publication Ethics (COPE). For additional information, please visit http://www.publicationethics.org. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access.

8. Secondary publication
It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, available at: www.icmje.org/.

9. Feedback after publication
If the authors or readers find any errors, or contents that should be revised, it can be requested from the Editorial Board. The Editorial Board may consider erratum, corrigendum or a retraction. If there are any revisions to the article, there will be a CrossMark description to announce the final draft. If there is a reader’s opinion on the published article with the form of Letter to the editor, it will be forwarded to the authors. The authors can reply to the reader’s letter. Letter to the editor and the author’s reply may be also published.

9-1. Process to manage the research and publication misconduct
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”.

Online access in http://ekja.org
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.
Leaves 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 (eg, .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 does not need to be included in the body of the manuscript but may be supplemented in an appendix.

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.

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.

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.

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. Exception) 5%, 36oC

- 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.

① Table
  · 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.

② 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 in recognizable 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-
GLISH 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., Vid-
eo 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 guar-
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 be exceed 100. For exceeding the number of references, it should be negotiated with the Editorial Board. Body text should not exceed 30 A4 pages, and the number of figures and tables should be equal to or less than 6.

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 anesthesia 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.
Multimodal analgesia is defined as the use of more than one pharmacological class of analgesic medication with the goal of improving analgesia while reducing drug-related side effects. Recently, various methods are used for multimodal analgesia. Elements may include opioids, non-opioid analgesics, and local anesthetics administered by regional block.

In the continuum of this endeavor to ensure patients’ well-being through proper pain control and drug-related safety, the Korean Journal of Anesthesiology (KJA) will publish a special issue devoted to the topic of “Multimodal Analgesia for Pain Management”. We welcome contributions that explore the advanced methods and innovative applications regarding the perioperative or postoperative pain management including new drugs or equipment application, regional block techniques and animal studies. These include both clinical and experimental research papers as well as systematic review of literatures.

**The deadline for submission is 30th June 2020.**

Please submit your papers to the homepage of KJA (https://www.editorialmanager.com/kja). Papers are published upon acceptance, regardless of the Special issue publication date and Special issue will be launched on Issue Number 5 of KJA 2020.

**Lead Guest Editor**

JAE HANG SHIM (Hanyang University College of Medicine, Seoul, Korea, jhshim@hanyang.ac.kr)