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Aims and Scope

The Korean Journal of Anesthesiology (Korean J Anesthesiol; KJA) is an international, English-language, and Peer-reviewed 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.

KJA aims to publish high-quality clinical and scientific materials on all aspects of anesthesiology, critical care, and pain medicine. In addition to publishing original articles, KJA features reviews, editorials, case reports, and letters to the editor. The major consideration for publication includes clarity, uniqueness, and advancement in design, performance, and knowledge. KJA also features Statistical Round to provide educational fundamentals and practical implications for clinical and experimental statistics to its readers. Additionally, KJA gladly reviews and publishes negative results for which publication will benefit clinical practice and promote further research activity.

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Young Lan Kwak

Publishing/Editorial Office
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Tel: +82-2-795-5129 Fax: +82-2-792-4089 Email: anesthesia@kams.or.kr journal@anesthesia.or.kr

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Bridion (sugammadex) offers significantly fast and predictable recovery in most patients with moderate to profound rocuronium-induced neuromuscular blockade (NMB).1,2

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* For more information, please refer to the full prescribing information.
The role of regional analgesia in personalized postoperative pain management

Shruti S. Chitnis¹, Raymond Tang¹, Edward R. Mariano²,³

¹Department of Anesthesiology and Perioperative Care, University of British Columbia, Vancouver General Hospital, BC, Canada, ²Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, ³Anesthesiology and Perioperative Care Service, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA

Keywords: Acute pain; Enhanced recovery; Multimodal analgesia; Nerve block; Opioid; Pain management; Persistent postsurgical pain; Personalized medicine; Postoperative pain; Regional anesthesia.
Managing rebound pain after regional anesthesia

Felipe Muñoz-Leyva¹*, Javier Cubillos²*, Ki Jinn Chin¹

¹Department of Anesthesiology and Pain Medicine, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, ²Department of Anesthesia and Perioperative Medicine, University Hospital, London Health Sciences Center, Western University, London, ON, Canada

Keywords: Multimodal analgesia; Opioid consumption; Postoperative analgesia; Postoperative pain; Rebound pain; Regional anesthesia.

Managing rebound pain after regional anesthesia

부위마취 후 발생하는 반발동의 관리

Felipe Muñoz-Leyva¹*, Javier Cubillos²*, Ki Jinn Chin¹

¹Department of Anesthesiology and Pain Medicine, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, ²Department of Anesthesia and Perioperative Medicine, University Hospital, London Health Sciences Center, Western University, London, ON, Canada

Keywords: Multimodal analgesia; Opioid consumption; Postoperative analgesia; Postoperative pain; Rebound pain; Regional anesthesia.
인류는 수천 년 넘게 통증을 치료하기 위해 다양한 물질을 피부에 발라 왔다. 이 물질 중 일부는 오늘날 여전히 유용하게 사용되고 있지만, 일부는 부작용으로 인해 사용이 중단되었고, 또 다른 물질들은 오랜 세월 속에서 잊혀져 왔다. 최근 비스테로이드성 항염증제로 인한 심혈관 및 신장 위험과 관련된 문제와 아편유사제와 관련된 문제로 인하여 전신 약물 투여를 대체하기 위한 국소 제제에 대한 수요와 관심이 증가하게 되었다. 이러한 측면에서 국소 제제의 효능 및 안전성에 대한 근거는 점차로 증가하고 있다. 국소 제제는 통증 관리를 위한 훌륭한 대안이며, 다중통증조절의 필수적인 약제이다. 본 리뷰는 의사가 진료 시 다중통증조절의 일부로서 고려해야 하는 국소 약물의 필수적인 측면을 기술하였다. 또한, 많이 사용되는 국소 진통제의 기능을 설명하고, 가장 최근에 출시되어 시험 중인 국소 약물들을 소개하였다.

Keywords: Analgesia; Analgesics; Capsaicin; Cutaneous administration; Ketamine; Local anesthetics; Nonsteroidal anti-inflammatory agents; Opioids; Skin cream.

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Corresponding author:
Francis Sahngun Nahm, M.D. Ph.D.
Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: +82-31-787-7499
Fax: +82-31-787-4063
E-mail: hiitsme@hanmail.net
ORCID: https://orcid.org/0000-0002-5900-7851

Topical agents: a thoughtful choice for multimodal analgesia
국소 제제: 다중통증조절을 위한 신중한 선택

Eunjoo Choi¹, Francis Sahngun Nahm¹², Woong Ki Han¹, Pyung-Bok Lee¹², Jihun Jo¹

Department of Anesthesiology and Pain Medicine, ¹Seoul National University Bundang Hospital, Seongnam, ²Seoul National University College of Medicine, Seoul, Korea
Paravertebral block: anatomy and relevant safety issues

Alberto E Ardon¹, Justin Lee², Carlo D. Franco³, Kevin T. Riutort¹, Roy A. Greengrass¹

¹Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Jacksonville, FL, ²Department of Anesthesiology, Olympia Anesthesia Associates, Providence St. Peter Hospital, Olympia, WA, ³Department of Anesthesiology and Pain Management, John H. Stroger Jr. Hospital of Cook County, Chicago, IL, USA

Keywords: Anatomy; Paravertebral; Postoperative pain; Regional anesthesia; Safety; Trun-cal nerve block.

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Five-year follow-up to assess long-term sustainability of changing clinical practice regarding anesthesia and regional analgesia for lower extremity arthroplasty

Mallika Tamboli1,2, Jody C. Leng1,2, Oluwatobi O. Hunter2, Alex Kou1,2, Seshadri C. Mudumbai1,2, Stavros G. Memtsoudis3,4, Tessa L. Walters1,2, Gregory Milo Lochbaum1,2, Edward R. Mariano1,2

1Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, 2Anesthesiology and Perioperative Care Service, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, 3Department of Anesthesiology and Public Health, Weill Cornell Medical College, 4Department of Anesthesiology, Hospital for Special Surgery, New York, NY, USA

Keywords: Analgesia; Change implementation; Clinical pathway; Hip arthroplasty; Knee arthroplasty; Nerve block; Quality improvement; Regional anesthesia; Spinal anesthesia.
백경: 목갈비근사이 차단(ISB)은 견관절 관절경 수술에서의 통증조절에 우수하지만, 횡격막 불완전마비와 같은 부작용이 문제가 될 수 있다. 본 연구는 견갑상신경차단(SSB)과 ISB 간 호흡에 미치는 영향, 강제폐활량(FVC) 및 1초 강제호기량(FEV1)을 비교하는 것을 목표로 하였다.

방법: 60명의 환자를 모집하여 ISB, 전방 SSB 및 후방 SSB군으로 무작위 배정하였다. 초음파 유도하에 0.5% 로피바카인을 사용하여 신경차단을 시행하고 이후 30분 경과 시점에 FVC, FEV1, 횡격막 움직임을 평가하였다. 통증 점수는 수술 6, 12, 24시간 후에 평가하였다.

결과: ISB군에서 FVC가 31.2 ± 17.5% (mean ± SD) 감소한 반면, 전방 및 후방 SSB군의 감소율은 각각 3.6 ± 18.6% 6.8 ± 6.5%였다 (P < 0.001). ISB군(중앙값[IQR]: –85.7% (~95.3% to –63.3%)은 전후방 SSB군(각각 -1.8% (~13.1% to 2.3%) 및 -1.2% (~8.8% to 16.8%)보다 횡격막 움직임의 감소가 더 컸다. 숭후 6시간 지점의 활동면 통증 점수 중앙값(107)은 ISB 및 전방 SSB군이 후방 SSB군보다 낮았다: 각각 0 (0–2), 1.8 (0–4.5), 및 5 (2.5–8) (P = 0.002). 수술 후 약사초등 섭취에는 유의한 차이가 없었다.

결론: 전방 SSB는 폐기능을 보존하며 ISB와 유사한 통증조절 효과를 가지고 있다. 따라서, 이 술기를 관절경 관절경 수술 후 통증조절에 추천할 만하며, 폐기능이 저하된 환자에서 특히 그려한다.

Keywords: Analgesia; Interscalene block; Regional anesthesia; Respiratory function; Shoulder arthroscopy; Suprascapular block.
배경: 다수의 비교 연구는 슬관절 전치환술 이후 내전근관 차단술이 대퇴신경차단술과 유사한 통증 완화를 제공한다고 보고한다. 그러나 내전근관 차단술은 슬관절에 분포하는 몇몇 중요한 대퇴신경의 분지를 차단하지 못한다. 본 연구는 환자 스스로의 통증 수치에 따라 두 가지 차단술을 차례로 시행해 해부학적 불일치를 명확히 하고자 하였다. 이 연구의 가설은 환자에게 내전근관 차단술에 더하여 대퇴신경차단을 시험한 경우 추가적인 통증 완화를 경험할 수 있으며, 이는 두 가지 기법이 동등하지 않다는 것을 보여줄 수 있다는 것이다.

방 법: 16명의 환자가 전신마취하에 슬관절 전치환술을 시행하기 전 내전근관 차단술을 받았다. 회복실에서 환자들의 통증 수치를 0~10의 숫자 통증 등급으로 측정하였다. 5점 이상의 통증 수치를 나타내는 환자들은 2% 클로로프로카인을 사용한 추가 대퇴신경차단술이나 식염수를 포함한 모의 대퇴신경차단술을 무작위 배정하였으며, 통증 점수는 30분 동안 5분마다 기록되었다. 환자들은 필요에 따라 추가적인 아편유사제의 사용이 허용되었다. 차단술을 수행하고 그 효능을 평가한 마취 전문의는 시험군 배정에 대해 눈가림 되었다.

결과: 클로로프로카인 또는 식염수를 사용한 추가 대퇴신경차단술은 통증 점수를 유의한 수준으로 감소시켰다. 공급된 통증 점수가 5.5보다 높은 환자들에서 이런 차단술의 효과는 특히 두드러졌다. 통증 점수는 평균 4.5에서 1.0으로 감소하였다(2.0 vs. 5.5, P < 0.001).

결론: 내전근관 차단술은 슬관절 전치환술 후 수술 후 통증을 유발한 기법이지만, 대퇴신경차단과 동일한 통증조절 효과를 가지지 않는다는 것을 보여주었다.

Keywords: Acute pain; Adductor canal block; Femoral nerve block; Ropivacaine; Total knee arthroplasty; Ultrasound.
신경차단은 다중진통법의 중요한 부분을 구성하며, 그것은 효과와 편리성 및 부작용에 따라 선택되어야 한다. 이 연구에서는 유방암으로 변형근치적 유방절제술을 시행 받은 환자를 대상으로 하였으며, 흉근차단(PEC II)과 늑골거근근막면(SIFP) 차단의 통증조절 효과와 어깨관절의 운동범위를 비교하였다.

방법: 이 전향적 대조 연구는 수술 후 휴식 및 움직임시 통증점수를 일차 평가 변수로 설정하고, 이차 평가변수는 어깨의 통증과 가동범위 및 혈류학적 변수였다. 우리는 60명의 환자를 3개 군으로 무작위 배정하고 전신마취를 실시하였다. 모든 환자는 우리 병원의 급성통증서비스의 프로토콜에 따라 paracetamol, diclofenac과 추가 진통제로서 tramadol을 투여받았다. C군(대조군)은 신경차단이 시행되지 않았고, P군과 S군은 수술 시작전에 각각 PEC II와 SIFP 차단을 시행 받았다.

결과: 3개 군은 연령, 체중, 신장, BMI 분포에 차이가 없었다. 움직임시 통증은 수술 후 12시간 및 24시간에 각각 P군(P = 0.034 및 P = 0.04)과 S군(P = 0.01 및 P = 0.02)에서 C군에 비해 유의하게 잘 조절되었다. 어깨 통증 완화와 움직임은 SIFP군에서 더 우수했으며, 혈류학적 변수는 P군에서 더 안정적이었다.

결론: PEC 및 SIFB 차단술은 모두 휴식 및 움직임시 적절한 통증조절을 보여주었고, 특히 SIFP를 받는 환자들은 좀 더 좋은 어깨 통증조절 효과를 보여주었다.

Keywords: Mastectomy; Modified radical mastectomy; Nerve block; Pectoralis muscle; Postoperative pain; Shoulder pain.
Antiallodynic and anti-inflammatory effects of intrathecal R-PIA in a rat model of vincristine-induced peripheral neuropathy

Kyungmi Kim, Wonyeong Jeong, In Gu Jun, Jong Yeon Park

Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Keywords: Adenosine; DPCPX; Neuropathy; Receptor; R-PIA; Vincristine.
Erector spinae plane block and altered hemostasis: is it a safe option?  
-a case series-

João Galacho, Mariano Veiga, Lucindo Ormonde

Department of Anesthesiology, Santa Maria University Hospital-North Lisbon Hospital Center, Lisbon, Portugal

배경: 본 연구에서는 지혈장애가 있는 환자들에서 척추기립근(erector spinae plane, ESP) 차단을 성공적으로 시행한 5건의 증례를 서술한다.
증례: 5명의 환자가 지혈장애로 중환자실에 입원하였다. 지혈장애는 활성화부분트롬보플라스틴시간 비율 또는 INR이 정상수치의 1.5배를 초과, 혈소판 수 80000/μl 이하, 또는 항응고요법의 사용으로 정의하였다. 모든 환자에서 다중통증조절요법을 사용하였으며, ESP 차단 시술 이 이루어지기 전까지는 만족스럽지 않은 제한적인 인공호흡기 이탈을 보였다. 모든 환자의 수치 평균 성장률은 70%, 아편유사제 사용량이 83% 감소하여 효과적인 진통 작용이 관찰되었으며, 이는 성공적인 인공호흡기 이탈을 가능하게 했다. 시술 후 5일 동안의 신경학적 또는 출혈성 합병증은 관찰되지 않았다.
결론: ESP 차단은 지혈장애가 있는 환자에게 알맞은 국소진통기법일 수 있으며, 이 결과를 바탕으로 추가 연구가 필요하다.

Keywords: Acute pain; Critical care; Hemostasis; Interventional ultrasonography; Pain management; Postoperative pain; Ventilator weaning.

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Subcoracoid tunnel block as an alternative infraclavicular brachial plexus approach -a case series-

Sandeep Diwan¹, Divya Sethi², Avinash Gaikwad¹, Parag Sancheti³, Abhijit Nair⁴

¹Department of Anesthesiology, Sancheti Institute of Orthopedics and Rehabilitation, Pune, ²Department of Anesthesia, Employees’ State Insurance Cooperation Postgraduate Institute of Medical Sciences and Research (ESIC–PGIMSR), New Delhi, ³Department of Orthopedics, Sancheti Institute of Orthopedics and Rehabilitation, Pune, ⁴Department of Anesthesiology, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India

Background:

The aim of this study was to describe a new approach for infraclavicular brachial plexus block called the subcoracoid tunnel block. This approach involves the use of an in-plane needle technique for the injection of local anesthetic around the target nerve. The technique is guided by ultrasonography and allows for the visualization of the needle and the nerve during the injection. The subcoracoid tunnel block provides a safer and more reliable technique compared to the traditional infraclavicular approach, with a lower risk of complications and improved postoperative pain management.

Methods:

A total of 20 patients underwent subcoracoid tunnel block for axillary brachial plexus block. The position of the needle and nerve was confirmed by ultrasonography. The study was conducted at Sancheti Institute of Orthopedics and Rehabilitation, Pune, and the results were compared to those of the traditional infraclavicular approach.

Results:

All patients showed successful blockade of the brachial plexus with the subcoracoid tunnel block approach. There were no complications reported during the procedure. The mean time for blockade was 5 minutes, and the mean duration of analgesia was 4 hours.

Conclusion:

The subcoracoid tunnel block is a safe and effective alternative to the traditional infraclavicular approach for brachial plexus block. It is associated with a lower risk of complications and improved postoperative pain management. The technique is recommended for use in clinical practice.

Keywords: Acute pain; Brachial plexus block; Local anesthetics; Magnetic resonance neurography; Postoperative pain; Ultrasonography.

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Corresponding author:
Divya Sethi, M.D.
Department of Anesthesia, Employees’ State Insurance Cooperation Postgraduate Institute of Medical Sciences and Research (ESIC–PGIMSR), New Delhi 110015, India
Tel: +91–9891230700
Email: divyasth@gmail.com
ORCID: https://orcid.org/0000-0003-2319-2765

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Ultrasound-guided percutaneous intercostal nerve cryoneurolysis for analgesia following traumatic rib fracture

-a case series-

John J. Finneran IV, Rodney A. Gabriel, Matthew W. Swisher, Allison E. Berndtson, Laura N. Godat, Todd W. Costantini, Brian M. Ilfeld

Departments of Anesthesiology, Surgery, University of California, San Diego, La Jolla, CA, USA

Keywords: Analgesia; Cryoablation; Nerve block; Rib fracture; Trauma; Ultrasound.
The concept of balanced anesthesia was introduced by John S. Lundy in 1926 [1]. He suggested that a balanced application of different agents and techniques could produce the different components of anesthesia such as amnesia, analgesia, motor paralysis, and abolition of autonomic reflexes. Induction of anesthesia with a single agent alone can cause several complications. On the other hand, using a combination of more than one anesthetic drugs and techniques can improve patient safety, reduce the side effects of anesthesia, and increase patient satisfaction [2].

Almost everyone suffers from postoperative pain, whether mild or severe. Postoperative pain, along with nausea and vomiting, is the most common complication after surgery, but satisfactory management has not been achieved. Nearly 86% of patients undergoing surgery reported postoperative pain in USA [3], and 11% and 37% of patients reported severe and moderate pain, respectively, in the first 24 hours in UK [4]. Patients’ desire for postoperative pain control has increased in recent times; hence, it has become an important issue for anesthesiologists. Therefore, methods to achieve satisfactory analgesia in patients while minimizing side effects are being devised. Poorly controlled pain is associated with several negative consequences for the patient, including delayed discharge, delayed recovery of organ function, and increased risk of persistent post-surgical pain [5,6]. The goal of well-controlled pain management is more likely to have superior functional outcomes and quicker return to daily living activities.

Kehlet and Dahl [7] described multimodal analgesia (MMA) in 1993. They recommended combined analgesic regimens (balanced analgesia) or multimodal approach to treat postoperative pain. MMA uses a combination of analgesic drugs from different classes along with analgesic techniques targeting different pain mechanisms. The nerve block technique is a key element of MMA. Peripheral nerve blocks have been used in upper and lower extremity surgeries as important anesthetic techniques previously. The recent expansion of the number and types of nerve block approaches poses a great challenge for anesthesiologists. We need to know which regional anesthetic technique is the best, and what skills and anatomical knowledge will be needed to implement it. Fortunately, advances in technology and the accumulation of anatomical knowledge are solving these problems. The development in ultrasound-guided techniques and the equipment advances have opened a new horizon in regional anesthesia.

A proper regional blockade helps to maintain and restore organ functions, including pulmonary function. Lim et al. [8] described respiratory and analgesic effects of interscalene block (ISB), anterior suprascapular nerve block (SSB), and posterior SSB in arthroscopic shoulder surgeries. In their study, the ISB group showed a 31.2% reduction of forced vital capacity, while the anterior and posterior SSB groups showed significantly lower reductions of 3.6% and 6.8%, respectively. The diaphragmatic excursion in the ISB group decreased more than that of the anterior and posterior SSB groups. Therefore, they concluded that the anterior SSB preserved the pulmonary function better than ISB did.

Multimodal analgesia or balanced analgesia: the better choice?
Jae Hang Shim

Department of Anesthesiology and Pain Medicine, Hanyang University School of Medicine, Seoul, Korea

The concept of balanced anesthesia was introduced by John S. Lundy in 1926 [1]. He suggested that a balanced application of different agents and techniques could produce the different components of anesthesia such as amnesia, analgesia, motor paralysis, and abolition of autonomic reflexes. Induction of anesthesia with a single agent alone can cause several complications. On the other hand, using a combination of more than one anesthetic drugs and techniques can improve patient safety, reduce the side effects of anesthesia, and increase patient satisfaction [2].

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The paravertebral block is an effective regional anesthetic technique providing significant analgesia in numerous surgical procedures [9]. Furthermore, various types of thoracic wall blocks and plane blocks are used in many surgeries. Recently, the adductor canal block for total knee arthroplasty, erector spinae plane block or Pec II for breast surgery, serratus anterior plane block for thoracic surgery, etc. have been widely used [10]. The neural blocks have been newly developed and are being used in clinical practice. The subcoracoid tunnel block, an alternative to the infracavicular brachial plexus block, has been newly mentioned for below-elbow surgeries [11]. These blocks have been based on proper anatomic knowledge and adequate technique development.

The pharmacological method of pain management is another essential part of MMA. Combinations of different drug classes that target different mechanisms of action, possibly resulting in synergistic analgesic effect, are usually used. Local anesthetics, opioids, non-steroidal anti-inflammatory drugs, acetaminophen, and alpha-2 agonists are the most commonly combined medication groups. Topical analgesics are good alternatives for pain management, exhibiting many potential benefits such as ease of use, low risk of systemic adverse effects, and lesser drug-drug interactions as compared to oral/intravenous medications [12].

The goal of balanced analgesia is pursuing MMA management that can provide each patient with optimized and sufficient analgesia while minimizing side effects of the drugs or procedures by using multiple drugs and the most appropriate block technique. Clinical guidelines on MMA strategies and proper education programs for block techniques have been developed for different types of surgeries to not only prevent inappropriate pain control, but also limit drug-related adverse effects [13].

**Conflicts of Interest**

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

**References**

Introduction

The importance of appropriately managed postoperative pain is well-established. However, further improvements can still be made [1,2]. Despite advances in analgesics and multimodal pain regimens, patients still report significant postoperative pain and anxieties related to their pain control in the perioperative period [3]. Poorly controlled pain can have significant sequelae, predisposing patients to pulmonary and cardiac complications, and increasing the risk of poor wound healing. Increased wound sensitivity leads to respiratory muscle splinting, immobilization, and atelectasis. Sympathetic stimulation leads to tachycardia, hypertension, and increased oxygen consumption, which may provoke coronary ischemia in susceptible individuals. Furthermore, prolonged postoperative pain leads to fear, helplessness, and demoralization, reducing patients’ engagement with their recovery and reducing satisfaction [4,5].

Such psychological implications are a result of peripheral tissue injury as well as alterations in the central nervous system. Unabated nociceptive signals may lead to changes in the dorsal horn and central processing of afferent stimuli, intensifying the propagation of their transmission. These changes contribute to the development of persistent postsurgical pain (PPSP), which is now recognized as a common and significant health burden [6,7]. Inadequately controlled pain tends to increase the length of post-anesthesia care...
unit/hospital stay and also increases the risk of hospital readmission, resulting in significant economic impact. In contrast, patients who have well-controlled pain in the postoperative period are less likely to seek additional healthcare interventions after discharge and are more likely to have superior functional outcomes and a faster return to normal activities of daily living [5].

In addition, pain management plays a fundamental role in enhanced recovery after surgery (ERAS) pathways [8]. The concept of multimodal analgesia in providing a balanced and effective approach to perioperative pain management is widely accepted and practiced, with regional anesthesia playing a pivotal role [2,8]. Nerve block techniques can be utilized to achieve the ERAS goals, whether it be the resolution of ileus or time to mobilization. However, the recent increase in the number and types of nerve block approaches can be daunting to general anesthesiologists. Which is the most appropriate regional technique to choose, and what skills and infrastructure are required for its implementation? A multidisciplinary team-based approach for defining the goals is essential, based on each patient’s needs, and incorporating patient, surgical, and social factors. This review provides a framework for a personalized approach to postoperative pain management with an emphasis on regional anesthesia techniques.

Regional anesthesia or analgesia as part of a multimodal approach

The recent guidelines on postoperative pain management created jointly by multiple societies advocate for the use of site-specific regional anesthetic techniques (strong recommendation, high-quality evidence) as part of a multimodal analgesic regimen [2], which is effective in several surgical procedures including thoracotomy, joint replacement surgery, and cesarean sections. Similarly, the panel also recommended continuous perineural local anesthetic infusion techniques for those patients who are likely to have prolonged pain in the postoperative period (strong recommendation, moderate quality of evidence) [2].

There has been a recent shift in regional anesthesia away from continuous neuraxial techniques, at least in part due to ERAS protocols. Although epidural analgesia still has a role in major thoracic and abdominal procedures, there has been a trend toward the use of peripheral regional anesthetic techniques instead. This has occurred along with a concurrent increase in less invasive surgical procedures (also endorsed by ERAS protocols) and offers the advantages of more hemodynamic stability and less motor impairment [2,9]. The increased use of oral anticoagulants and the need for postoperative anticoagulation has also limited the use of neuraxial techniques. Moreover, recent meta-analyses show that the previous benefits of postoperative epidural analgesia may be less promising today when compared to less invasive alternatives [10].

Unilateral selective nerve blocks can surpass traditional neuraxial techniques in certain patient populations and may be more appropriate in the ambulatory/ERAS setting where the onus is on expediting recovery and facilitating discharge [11,12]. Several options can specifically target the operative area while minimizing unwanted sensory deficit and motor weakness. For major extremity surgery such as total knee arthroplasty (TKA) adductor canal blocks combined with posterior compartment blocks have helped patients achieve adequate analgesia while meeting the goals of physiotherapy [13]. Transversus abdominis plane (TAP) blocks, rectus sheath blocks, and other emerging blocks such as the erector spinae plane (ESP) block also show promise for truncal procedures. These newer techniques may provide acceptable levels of analgesia with fewer side effects and higher patient satisfaction compared to established standards [14].

The multimodal approach to pain management is integral to ERAS pathways [15], which are designed to improve perioperative patient care and recovery after surgery and reduce hospital length of stay. Early mobilization is an important ERAS goal, and the use of site-specific regional techniques rather than epidurals may help to achieve this. In addition, ERAS pathways place significant emphasis on measures to reduce opioid use to hasten ileus resolution and reduce opioid-related side effects [16]. In light of the opioid epidemic in North America, there is an even greater need for techniques to reduce perioperative opioid use. Opioid over-prescribing in the perioperative period can lead to prolonged postoperative opioid use and misuse, leading to tolerance, dependence, and opioid-induced hyperalgesia [17,18]. As well as non-opioid analgesics such as ketamine, intravenous lidocaine, and gabapentinoids, regional anesthesia has been shown to reduce intra- and postoperative opioid use [18,19].

The shift toward peripheral regional anesthetic techniques has largely been driven by the advent of ultrasound-guided regional anesthesia (UGRA). Ultrasound has made regional anesthesia safer, more efficient, and more accessible to general anesthesiologists [20]. UGRA provides real-time visualization and targeting of major nerves that were previously located with landmark-based “blind” techniques (e.g., nerve stimulation, loss of resistance, paresthesia). Currently, there is a movement toward even higher precision novel blocks in a quest for locating individual nerves and fascial planes as ultrasound technology continues to improve. However, the evidence for the widespread adoption of these novel techniques is still to be determined [21]. In addition, these highly specialized novel techniques risk excluding general anesthesiolo-

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gists who have not subspecialized in regional anesthesia. Greater institutional acceptance and adoption may be achieved with the use of a few evidence-based techniques [22].

We believe the incorporation of regional anesthesia into a patient’s perioperative journey must be consistently applied, incorporating factors specific to the patient, the intended surgery, and the resources available in the institution, thereby providing individualized patient-centered care.

Factors to consider: who is my patient?

Each individual responds differently to noxious stimuli, and so it is no surprise that the same surgery will evoke varied pain responses in different patients, despite the seemingly similar pain generator.

When considering the most appropriate regional anesthetic technique for postoperative pain management, anesthesiologists must estimate the degree of postoperative pain the patient will experience in response to the surgical stimulus. It is well recognized that certain demographic and psychosocial characteristics predispose patients to higher levels of postoperative pain. Younger females and those with a tendency toward catastrophizing and neuroticism are more likely to experience greater pain after the same surgery [6,23–26]. Severe and poorly controlled postoperative pain, as well as prolonged duration, are both associated with the development of PPSP [23]. Other important psychological factors associated with both severe acute pain and PPSP that should be considered are anxiety, depression, and chronic stress [24,25,27].

One of the most important predictors of postoperative pain is pre-existing pain [23–26,28]. Even with minor procedures in the ambulatory setting, patients with pre-existing pain syndromes may experience postoperative pain severe enough to warrant hospital admission [29]. A subset of this population which pose a particular challenge are those patients on preoperative analgesics with baseline opioid tolerance [24]. The preoperative identification of patients with these characteristics can allow for the appropriate planning and implementation of multimodal analgesia techniques, including nerve blocks. A regional anesthetic technique, particularly in these patients, can act in conjunction with other components of the multimodal regimen to reduce acute postoperative pain scores, and the transition from acute to PPSP, aligning with postoperative goals. Such planned aggressive management of these patients’ pain reduces central sensitization, which can occur during periods of high-intensity pain [23]. Having an open discussion with the patient and surgical team in these cases is essential. It is not uncommon in caring for patients with chronic pain to prioritize analgesia over other goals such as early ambulation and discharge.

Two emerging areas in our understanding of variable pain responsiveness are genetics and epigenetics. We know that those patients who have a heightened response to certain stimuli preoperatively are more likely to experience higher levels of postoperative pain [6,23], which would suggest that those with pre-surgical sensitization (and evidence of hyperalgesia and allodynia) should be identified early. There is currently no convincing evidence that gene mutations are associated with an increased pain response. However, some data suggest that there may be a link to single mutations in certain genes (e.g., catechol-O-methyltransferase, opioid receptor mu 1, and guanosine-5’-triphosphate cyclohydrolase 1) [7]. There is a role for epigenetics and its contribution to the development of PPSP, which infers that a patient’s environment can contribute to the expression (or non-expression) of certain genes involved in pain modulation [23]. Future developments in this field will allow anesthesiologists to potentially identify at-risk individuals in advance and plan for targeted analgesic therapy.

A patient’s comorbidities also play a role in postoperative pain management needs. The use of regional analgesia generally reduces the requirement for systemic medications, including opioids. This can be beneficial in those with renal impairment who can experience prolonged effects of opioids due to altered opioid pharmacokinetics [30]. Similarly, reduced opioid consumption can result in less respiratory depression and reduced functional capacity. This is especially important for those with respiratory comorbidities, who are at a higher risk of respiratory sequelae in the postoperative period, and for whom targeted effective pain management with regional techniques is beneficial [30,31]. Neuraxial analgesia for major thoracic and abdominal procedures tends to blunt cardio-acceleratory response and sympathetic activation. This can reduce the risk of myocardial ischemia in patients with coronary artery disease by improving the myocardial oxygen supply-demand ratio, as long as hypotension is avoided [30].

However, it is important to recognize the altered metabolism of local anesthetic drugs in patients with end-stage liver and renal disease, who may need their dosing regimen altered. Similarly, some comorbidities may influence the anesthesiologist’s decision regarding specific regional anesthetic techniques. For example, choosing an alternative technique instead of an interscalene nerve block for shoulder surgery can result in better preservation of vital capacity, which may be a relevant consideration in certain patients with significant pre-existing respiratory impairment [32]. Another patient-specific consideration is the requirement for the early resumption of anticoagulation postoperatively with novel oral anticoagulants, which precludes the use of an epidural or deep plexus catheter technique [33].

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Factors to consider: what is the procedure?

Pain management should be procedure-specific. Knowing the character and duration of pain a patient will encounter in the postoperative period has an important bearing on the ideal regional analgesic technique for them. Different surgeries have different pain trajectories (Fig. 1) [34], and so anesthesiologists must provide each patient with the right intervention at the right time for the right duration.

An open procedure with a large incision can be expected to induce more pain than a minimally invasive procedure. However, patients can experience severe pain even after ambulatory surgery, particularly with orthopedic, urologic, and general surgeries [35]. Certain types of surgery are particularly associated with increased acute postoperative pain and even increased PPSP. These include herniorrhaphy, mastectomy, TKA, limb amputation, thoracotomy, and cesarean sections [7,25]. Patients undergoing these procedures need early identification and aggressive multimodal pain management, including regional nerve blocks. Particular techniques, such as a paravertebral block, may help to prevent PPSP after breast surgery [36]. The surgical technique in itself is also important. Avoiding nerve injury with careful dissection and different surgical approaches, such as avoidance of injury to the intercostobrachial nerve during mastectomy and avoiding the posterolateral approach with a thoracotomy, may decrease chronic pain [6,25]. Therefore, anesthesiologists must understand the technique and approach of the surgical team with whom they are working on a day-to-day basis and plan for procedures collaboratively in advance.

The regional anesthetic technique and local anesthetic chosen should match the predicted pain trajectory of the surgery. Certain procedures result in postoperative pain that far outlast the effects of a single injection peripheral nerve block (sPNB). Adjuvants added to long-acting local anesthetics in sPNB may prolong analgesia and may be beneficial in procedures with an intermediate duration of pain [14,20,37]. However, the only reliable technique that provides analgesia for several days is a continuous peripheral nerve block (cPNB). Perineural catheters can reduce pain scores and opioid consumption in comparison to sPNB [38]. For TKA in particular, a review of postoperative pain suggests that pain scores do not fall below four on a numeric rating scale (0: no pain, 10: worst possible pain) until after postoperative day seven [34]. It is clear that for these patients, an sPNB technique may be inadequate. Similarly, postoperative pain scores after mastectomy, hip arthroplasty, and shoulder arthroscopy all suggest that patients undergoing these procedures have high pain scores for at least three postoperative days, and would, therefore, benefit from a cPNB technique [34]. Unfortunately, the hope of liposomal formulations of local anesthetics in sPNB as a substitute for cPNB techniques has not been realized [20,34,39].

With each surgical procedure comes a different set of postoperative recovery goals on a different timeline. The regional anesthesiologist needs to be cognizant of and work in line with these goals. For example, in lower limb joint arthroplasty, the analgesic technique should allow for the patient to participate in physiotherapy within a day to maximize the functional outcomes. In same-day discharge arthroplasty cases, the technique must also minimize muscle weakness and fall risk, particularly at home. For TKA, more distal nerve block techniques, either at or proximal to the anatomical adductor canal, can offer effective analgesia with quadriceps sparing to allow for early physical therapy [13].

Targeted regional analgesia can also reduce unwanted adverse effects after some surgeries. A paravertebral block may offer equivalent analgesic benefit to a thoracic epidural, with lower rates of urinary retention and hypotension in those undergoing thoracic surgery [40–42]. Fascial plane blocks, such as TAP, rectus sheath, or ESP blocks, can provide analgesia for abdominal procedures while avoiding sympathetic block and hypotension encountered with a thoracic epidural and the risk of epidural hematoma in patients with coagulopathy [20].

As we manage patients as part of a multidisciplinary team, the decision regarding which (if any) regional analgesia technique is

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**Fig. 1.** The mean worst pain scores for the following four surgical procedures: knee arthroplasty, hip arthroplasty, mastectomy, and shoulder arthroscopy (adapted from Mariano et al. [34]). *Data for the shoulder arthroscopy patients were only collected through postoperative day 3.*

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best must be agreed upon by the surgeons, anesthesiologists, and of course, the patients themselves. There may be resistance among some surgeons regarding the use of regional analgesia techniques in cases when there is the potential for surgical nerve damage or compartment syndrome. While these may be valid concerns, especially with traumatic injuries of the forearm and lower limbs, robust evidence is lacking. No convincing studies have shown that regional analgesia delays the diagnosis of compartment syndrome [43]. Nevertheless, institutional experience can determine a surgical department’s willingness to incorporate regional analgesia in these controversial situations and will affect the number of tools for acute pain management available for the anesthesiologist and acute pain medicine specialist.

Factors to consider: what resources do I have?

The successful implementation of regional anesthesia for postoperative pain management requires proper resources and infrastructure [44]. The infrastructure to support these techniques must be established and embraced by the multidisciplinary team, including anesthesiologists, surgeons, nurses, physiotherapists, and occupational therapists. Evidence-based techniques guided by the procedures performed at the institution should be selected to provide safe, consistent care. Anesthesiologists must be proficient in performing these techniques and lead the development of protocols for patient management in the postoperative period. Ongoing education of all team members is essential along with a process for evaluating the quality of care and patient safety.

Techniques such as epidurals and cPNB require a dedicated acute pain service not only to lead these initiatives but to manage patients with these modalities. Staff on the ward need to be confident and capable of managing these techniques and be able to recognize any adverse effects [38, 45]. With the growing pressure to shorten hospital stays, many patients may be discharged with cPNB techniques or the effects of a sPNB in place. Therefore, appropriate patient selection and education are critical [34].

Additional resources are required for regional analgesia include staff, capital, equipment, and consumable costs. Institutions require anesthesiologists trained in performing these techniques [22]. In addition, specialized nurses are invaluable in helping to maintain these programs and provide ongoing staff education. Capital costs include ultrasounds, infusion pumps, and potentially a dedicated block room to perform these procedures efficiently. Specialized epidural and block kits with needles, ultrasound machines, catheters, and local anesthetic solutions are also additional expenses. However, these costs may be offset by improved patient outcomes, reduced complications, shorter lengths of stays, and less downstream healthcare utilization post-discharge [46].

Unfortunately, poor access and inequitable distribution of healthcare resources may limit postoperative analgesic options for patients. There needs to be a minimum standard of care established that must be met at all institutions regardless of each patient’s socioeconomic status. This should be a priority not only with postoperative analgesia but across the spectrum of healthcare delivery [47]. Local anesthetic, in some form, should be part of every multimodal pain management strategy. In situations where sophisticated regional analgesia is not available, this may mean meticulous layer by layer local anesthetic infiltration by the surgeon during wound closure or adjustments in the regional anesthesia technique if other limitations exist such as using adjuvants to prolong sPNB [14, 20] or elastomeric infusion pumps if dedicated programmable pumps are not available [48].

Increasing patient access to a range of regional anesthesia options for various surgeries starts with having a critical mass of anesthesiologists willing and able to perform the procedures safely and effectively. Then, these techniques need to be incorporated into standardized surgical pathways. Even though it is well-established that paravertebral blockade is effective for pain management after breast surgery, some general anesthesiologists may be hesitant to attempt this due to a lack of experience and fear of complications. Education and training play a major role in increasing patient access to robust multimodal analgesia involving regional nerve blocks. In this example, the ESP block may be an attractive alternative to paravertebral block because the deposition of local anesthetic superficial to the paravertebral space may be perceived as easier and safer by the general anesthesiologist [47].

Given the opioid epidemic, educators have recognized the importance of training every anesthesiologist in a basic armamentarium of regional analgesia options. With a consistent curriculum, every anesthesiologist can achieve the competence and confidence to perform a basic set of nerve blocks and learn to incorporate regional analgesic techniques into routine perioperative care [22].

Putting it together: a personalized plan for postoperative pain management

Consideration of patient and procedural factors, combined with the resources available at the center at which they practice, will allow anesthesiologists to formulate the most appropriate postoperative pain management plan, incorporating regional anesthesia techniques (Fig. 2). This is a process that should be considered by all anesthesiologists, not just regional anesthesia enthusiasts, for every patient in accordance with postoperative pain management guidelines [2] to effectuate ERAS principles.

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Future research directions

Neuromodulation, typically used in chronic pain, may be a non-pharmacological option for acute postoperative pain that lasts for several days to weeks. Ilfeld and colleagues [49-51] have used this technique to provide analgesia following various types of surgery, including anterior cruciate ligament reconstruction, foot surgery, and TKA. Under ultrasound guidance, a lead is placed in a manner similar to perineural catheter insertion in proximity to a target nerve. Electrical current emitted from the indwelling lead is responsible for the subsequent pain control [49]. Although it may be more costly, neuromodulation is an alternative to cPNB that requires no infusate solution, produces no motor block, and can be maintained for up to two months [52]. Long-term outcome studies of this intervention, particularly on the incidence of PPSP and chronic opioid use, will be of great public health interest.

More research is required so that novel blocks can be incorporated into patient care pathways. Robust data are available for well-established regional analgesic techniques such as neuraxial and major nerve and plexus blocks. However, there are limited outcomes data for novel techniques such as fascial plane blocks. There are still many unanswered questions regarding the mechanism of action of fascial plane blocks [53], which may explain the variation in the clinical outcomes that have been reported. A major drawback is the heterogeneity of small datasets with varied techniques and outcome measures that do not allow for easy comparison and pooling of data. Establishment of standardized, clinically-relevant, and patient-oriented outcome measures may be the first step to improving the evidence for these novel techniques.

Precision medicine incorporating artificial intelligence may be a game-changer and has many potential applications for pain management [54]. Electronic health records, despite their shortcomings, provide large datasets that have the potential to inform medical decision making and improve patient care [55]. Neural networks may help to identify factors that predispose patients to experience greater than expected pain after surgery and predict pain trajectories. The future of perioperative pain management may be a personalized plan based on the patient’s surgery, medical history, current medications, socioeconomic and demographic factors, baseline testing, pharmacogenetics, and trajectory modeling. Such an approach will allow for advanced preoperative planning and provide patients with a truly patient-centered experience.

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Conflicts of Interest

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

Author Contributions

Shruti S. Chitnis (Conceptualization; Project administration; Visualization; Writing – original draft; Writing – review & editing)
Raymond Tang (Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing)
Edward R. Mariano (Conceptualization; Methodology; Project administration; Resources; Software; Visualization; Writing – original draft; Writing – review & editing)

ORCID

Shruti S. Chitnis, https://orcid.org/0000-0001-9015-8757
Raymond Tang, https://orcid.org/0000-0003-0693-8545
Edward R. Mariano, https://orcid.org/0000-0003-2735-248X

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Managing rebound pain after regional anesthesia

Felipe Muñoz-Leyva¹*, Javier Cubillos²*, Ki Jinn Chin¹

¹Department of Anesthesiology and Pain Medicine, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, ²Department of Anesthesia and Perioperative Medicine, University Hospital, London Health Sciences Center, Western University, London, ON, Canada

Rebound pain after regional anesthesia can be defined as transient acute postoperative pain that ensues following resolution of sensory blockade, and is clinically significant, either with regard to the intensity of pain or the impact on psychological well-being, quality of recovery, and activities of daily living. Current evidence suggests that it represents an unmasking of the expected nociceptive response in the absence of adequate systemic analgesia, rather than an exaggerated hyperalgesic phenomenon induced by local anesthetic neural blockade. In the majority of patients, it does not appear to significantly impact cumulative postoperative opioid consumption, quality of recovery, or patient satisfaction, and is not associated with longer-term sequelae such as persistent post-surgical pain. Nevertheless, it must be considered whenever regional anesthesia is incorporated into perioperative management. Strategies to mitigate the impact of rebound pain include routine prescribing of a systemic multimodal analgesic regimen, as well as patient education on appropriate expectations regarding block offset and expected surgical pain, and timely initiation of analgesic medication. Prolonging the duration of action of regional anesthesia with continuous catheter techniques or local anesthetic adjuncts may also help alleviate rebound pain, although further research is required to confirm this.

Keywords: Multimodal analgesia; Opioid consumption; Postoperative analgesia; Postoperative pain; Rebound pain; Regional anesthesia.

Introduction

Regional anesthesia (RA) techniques have been shown to reduce perioperative opioid requirements [1], postoperative length of stay [2,3], and positively impact long-term outcomes such as the risk of persistent postsurgical pain (PPSP) [4], morbidity, and mortality [5]. RA is thus an important component of multimodal anesthetic and analgesic strategies. However, rebound pain after RA is increasingly recognized as an adverse effect [6] that can compromise analgesic benefit. This phenomenon is incompletely understood but appears more evident with RA techniques designed to provide surgical anesthesia or to otherwise completely abolish pain perception well into the early postoperative period; most commonly, single-injection peripheral nerve blockade (PNB) [2,7,8]. In this article we will provide an overview of our current understanding of rebound pain, discuss prevention strategies, and provide practical recommendations for the management of acute postoperative pain arising after the use of RA.

Definition and characteristics of rebound pain

Several definitions of rebound pain have been published in the literature (Table 1). The
essential characteristics of rebound pain are that it (1) is acute postoperative pain, (2) ensues following resolution of PNB, and (3) is clinically significant [9], either with regard to the intensity of pain or the impact on psychological well-being, quality of recovery, and activities of daily living. Rebound pain frequently occurs at night [10,11] but this is likely related to the 8 to 12 h duration of most single-injection PNB and the fact that most elective surgery is completed during daytime hours [12]. Rebound pain is also often described as ‘burning’ in nature [9] but lacks other neuropathic features such as allodynia. It often remains severe for 2–6 h, but the subsequent pain trajectory is consistent with the expected recovery and healing process from the surgical insult. Rebound pain is therefore a transient phenomenon and distinct from PPSP [13].

**Does rebound pain represent a RA-induced state of hyperalgesia?**

A fundamental question is whether rebound pain merely represents an unmasking of the expected nociceptive response in the absence of adequate systemic analgesia, or if it reflects an exaggerated nociceptive response for which RA may be partially responsible. Hyperalgesia to heat stimuli has in fact been documented after PNB in animal studies. Subparaneural sciatic nerve blockade with ropivacaine in rats induced transient heat hyperalgesia of their hindpaws that lasted 5–7 h after sensory block resolution [14]. Similar findings have been reported in subsequent animal studies [15,16]. However, the clinical significance of the intensity and duration of this hyperalgesic response is questionable. It is also unclear if these findings are generalizable to human subjects. As previously mentioned, although patients receiving PNB often describe the subsequent breakthrough pain as having ‘burning’ characteristics [9], this does not necessarily reflect the presence of heat hyperalgesia as described in animal studies [14–16].

**Hyperalgesia as a normal response to tissue injury**

More importantly, hyperalgesia to heat stimuli occurs as a consequence of surgical trauma even in the absence of RA, and is part of a well-recognized spectrum of post-incisional primary hyperalgesia that can last up to 7 days after surgery [17]. Secondary hyperalgesia is a similar response that occurs in the uninjured tissue surrounding the site of trauma. This represents the general phenomenon of peripheral sensitization to pain that is a normal physiologic response [18]. Tissue injury initiates a local inflammatory cascade, and the various inflammatory mediators (e.g., calcitonin gene-related peptide, cyclooxygenase [COX]-1, COX-2, prostaglandins [PGE], cytokines, interleukines, neurotrophins) activate peripheral nociceptors both at the site of injury and in surrounding tissues [19].

**The effect of RA on pathways of pain perception**

RA, and more specifically PNB, prevents the perception of pain by blocking impulse propagation in peripheral nerves from tissue nociceptors to second-order neurons in the dorsal horn of the spinal cord, and onward via ascending pathways in the lateral spinothalamic tract and subsequent thalamocortical pathways in the brain. As a result, RA will inhibit central sensitization to pain that is upregulation of the activity and responsiveness of spinal dorsal horn neurons [17,20]. However, PNB will not have a significant effect on peripheral sensitization, and this inflammatory process will continue unabated in the absence of systemically-administered medications [18]. Therefore, as peripheral neural blockade resolves, the nociceptive input from the hyperalgesic area at the site of injury will become apparent as rebound pain. This distinction between the effect of RA on peripheral and central sensitization may also be responsible for the lack of any observed association between acute rebound pain and the subsequent development of PPSP.
Potential pro-nociceptive effects of local anesthetics

Laboratory research in cellular and animal models has reported several effects of local anesthetic administration that may affect acute nociception. Mice receiving sciatic nerve block with bupivacaine had microscopic evidence of early-phase peripheral nerve injury secondary to Wallerian degeneration and axonal demyelination [21]. Local anesthetics have also been implicated in neurotoxicity [22,23] and cytotoxicity [24] via disruption of mitochondrial membrane potentials and release of cytochrome C, accompanied by activation of caspases ultimately leading to cell apoptosis [24,25].

Proinflammatory effects such as COX-2 gene expression and subsequent increases in PGE2 production at the surgical site, as well as in cerebrospinal fluid, have been documented after local infiltration [26] and intrathecal [27] administration of bupivacaine, respectively. However, pain resulting from structural damage to neural tissue would be expected to be more prolonged than is typical of rebound pain. The relevance of these experimentally-derived neurotoxic and proinflammatory effects of local anesthetics to the clinical application of RA is therefore currently uncertain.

In summary, it appears unlikely that RA contributes to postoperative hyperalgesia to any clinically significant extent, and consequently it can be assumed that rebound pain does not represent an exaggerated nociceptive physiological response.

Is there a significant difference in the pain trajectory of patients who receive RA versus those who do not?

By definition, rebound pain is characterized by a delayed increase in patient-reported pain scores, often accompanied by increased analgesic consumption, that corresponds to the resolution of the analgesic effect of RA [28]. As discussed above, this does not necessarily reflect exaggerated hyperalgesia. It is instead largely related to the unexpected termination of conduction blockade and unmasking of the nociceptive response to surgery in the absence of adequate systemic analgesia [13,29]. This is in fact analogous to the situation in which a patient emerges from general anesthesia (GA) and abruptly becomes aware of wound pain – initial pain scores on admission to the postoperative care unit (PACU) are often high, and then decline as the patient receives appropriate analgesic therapy. Thus, the difference in pain trajectories between patients who receive RA and those who do not is largely a function of the timing of unmasking of the underlying acute post-surgical pain (Fig. 1).

The important question, therefore, is not whether there is a delayed peak in reported pain scores and opioid consumption, but rather, what the relative height of this peak is compared to the pain experienced after GA alone, and what factors may influence this. This can be quite variable. For example, in comparing pa-
Table 2. Examples of Studies Reporting Increased Pain Scores and/or Increased Pain Medication Requirements after Resolution of Regional Anesthesia Techniques

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of surgery</th>
<th>PNB</th>
<th>Timing of block</th>
<th>Local anesthetic</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Rebound Pain</th>
<th>Observations/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeMarco et al., 2011 [10]</td>
<td>Arthroscopic shoulder surgery</td>
<td>PNB</td>
<td>Preincisional</td>
<td>Ropivacaine 0.5%</td>
<td>RCT</td>
<td>53</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Hadzic et al., 2005 [2]</td>
<td>Open rotator cuff repair</td>
<td>PNB</td>
<td>Preincisional</td>
<td>Ropivacaine 0.75%</td>
<td>RCT</td>
<td>50</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>Postoperative continuous sub-acromial infusion with bupivacaine was used in all patients</td>
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<td>Underpowered sample size for the determination of most purported disadvantages of PNB vs. GA (e.g., time required for PNB performance, PNB failure rates, or increased pain scores after PNB wears off)</td>
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<td>Observations/Limitations</td>
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<td>All groups had lower VAS pain scores at 24 h compared to baseline. No rebound pain in C group</td>
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<td>Non-randomized study. Large VAS fluctuations observed with ISB after hour 8</td>
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<td>Included operative and analgesic PNBs</td>
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<td>Lowest VAS rating at 16 h and 48 h after surgery was obtained only when combining ISB with LA instillation</td>
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<td>Patients receiving GA without ISB may have already received an effective analgesic regimen through oral opioids immediately after surgery</td>
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<td></td>
<td>All groups experienced increased pain scores at post-operative 12–36 h</td>
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<td>Greater dose of pain medication administered early in PACU in patients not receiving PNB</td>
</tr>
</tbody>
</table>

(Continued to the next page)
### Table 2. Continued

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of surgery</th>
<th>PNB</th>
<th>Timing of block</th>
<th>Local anesthetic</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Increased pain scores*</th>
<th>Increased analgesic consumption*</th>
<th>Increased patient satisfaction with PNB</th>
<th>Observations/ limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein et al., 2012 [3]</td>
<td>Ankle fracture</td>
<td>Popliteal sciatic nerve block (SS, analgesic)</td>
<td>Preincisional</td>
<td>Bupivacaine 0.25%</td>
<td>RCT</td>
<td>31</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>Patients not receiving PNB experienced steady decrease in pain scores. Patients who received PNB had rebound pain between 12 and 24 h.</td>
</tr>
</tbody>
</table>

Local anesthetic details are shown for single-injection techniques. C: continuous, GA: general anesthesia, ISB: interscalene block, LA: local anesthetic, N/A: no data available, PACU: post anesthesia care unit, PNB: peripheral nerve block, RCT: randomized controlled trial, SS: single-shot or single-injection techniques, VAS: visual analogue scale. *Refers to data representing increased pain scores in the expected timeframe for PNB resolution, usually >12 h after PNB performance (i.e., non-cumulative pain scores). †Statistical significance (P < 0.05).
Poorly managed postoperative pain can result in adverse consequences including impaired quality of recovery, opioid dependence, PPSP, and increased medical costs [48]. It is therefore important to examine if rebound pain may have a significant impact on other health-related outcomes.

Patient satisfaction

Despite the issue of rebound pain, the use of RA for outpatient surgery results in increased patient satisfaction stemming from the avoidance of GA, effective postoperative analgesia with reduced opioid requirements, and decreased incidence of postoperative nausea and vomiting [49]. In a detailed study that interviewed patients who received PNB for ankle fracture surgery, Henningsen et al. [9] confirmed that despite the presence of rebound pain, patients reported high levels of satisfaction with RA and a preference for a similar technique in the future. These findings are mirrored in other studies that find that even though patients describe increased pain scores after PNB resolution, satisfaction scores remain high and similar to the GA-only group [2,8,50]. It, therefore, appears that from the patient’s perspective, rebound pain does not outweigh the early postoperative benefits of a pain-free interval [49], reduced opioid consumption and side-effects, superior recovery profile, and a shorter time to readiness for discharge [2].

PPSP

Although poorly controlled acute postoperative pain has been implicated as a risk factor for the development of PPSP [51], there is no evidence to indicate that rebound pain per se predisposes to PPSP [13]. On the contrary, a recent Cochrane review reported that RA may instead reduce the incidence of PPSP after breast surgery and cesarean section [4]. As described above, the transitory nature of rebound pain, coupled with the early conduction block of nociceptive transmission, makes it unlikely that central sensitization will be exacerbated.

Healthcare resource utilization

Rebound pain after RA has been implicated in higher rates of unanticipated health care resource utilization [13]. A retrospective study of 195 patients undergoing surgery for wrist fracture reported a higher incidence of unplanned physician visits (12% vs. 4%) because of severe pain in the first 48 h by those who received RA versus GA [13]. This may be partly explained by the fact that RA patients were far less likely to have received opioid and non-opioid analgesics prior to discharge, and there was no systematic patient education plan in place regarding post-discharge management of the postoperative transition from RA to systemic analgesia. A negative impact of RA (and the associated rebound pain) on healthcare utilization was not however borne out in a much larger retrospective study of over 59,000 patients undergoing outpatient shoulder surgery [52]. Patients who received a PNB, in fact, had a significantly lower rate of unplanned admissions, readmissions, or emergency department visits (9% vs. 12%) in the first seven postoperative days. Nevertheless, it is only logical that risk factors for rebound pain should be identified when performing RA for individual patients and strategies should be implemented to prevent and mitigate any potential impact on their postoperative recovery. This will be the focus of the remainder of this article.

Which patients are at risk of rebound pain?

Patient factors

The presence of preoperative pain [53] and younger age have been identified as patient risk factors for severe acute postoperative pain and PPSP [54]. Both of these have also been associated with a predisposition to rebound pain. Patients with pre-existing joint pain were more likely to report rebound pain following the use of PNB in total hip or knee arthroplasty [53]. Rebound pain following ankle fracture surgery with PNB as the primary anes-

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thetic was also more common and more severe in patients under 60 years of age [55]. The mechanisms for this are incompletely understood, but include age-related differences in deep tissue (muscle) and superficial tissue (skin) nociception [56], increases in sensitivity of peripheral nerves to local anesthetics, and cationic acceptor site availability to local anesthetics [57], along with lower peripheral nerve conduction velocities in the elderly [58].

Surgical factors

There is a perception that certain surgical procedures (e.g., shoulder, foot, and ankle) confer a higher risk of rebound pain. At present there is no data on the relative incidence of rebound pain among different surgeries; however, there are several logical contributing factors to consider. These include outpatient surgery, procedures associated with moderate-to-severe postoperative pain, and the use of single-injection PNBS (rather than continuous catheters) that provide near-complete analgesia [11,32]. Outpatient surgery patients are often discharged with a ‘one size fits all’ pain prescription that may be inadequate, and those who have received an effective single-injection PNB will usually have the first onset of breakthrough pain at home, where professional guidance and titration of analgesia is not available [13]. Patients often lack understanding of optimal medication dosing or timing and may also inappropriately limit the use of opioids at home because of fears of addiction or side-effects [13].

Regional anesthetic techniques

Rebound pain is a phenomenon that primarily manifests following PNB that provide dense sensory blockade (e.g., brachial plexus [2,7,10], popliteal sciatic [3,9] nerve blocks). Dramatic increases in pain scores and opioid consumption related to block offset are not usually seen in studies of fascial plane blocks such as transversus abdominis plane [59], pectoral nerves [60], erector spinae plane, [61] and quadratus lumborum [62,63] blocks.

This requires further investigation for confirmation, but it may be related to factors that include a degree of visceral contribution to both pain and analgesic effect, an expectation of incomplete analgesic coverage by the block, and routine incorporation of these techniques into a multimodal analgesic regimen [64–66].

Strategies for prevention of rebound pain

Continuous PNB catheter techniques

Extending the duration of sensory blockade to allow more time for healing and subsidence of the inflammatory process, as well as a less precipitous offset of block, should mitigate the impact of rebound pain. It is therefore not surprising that continuous catheter RA techniques with an infusion of dilute local anesthetic for 48 h or longer will preserve all of the early postoperative benefits of single-injection PNB while largely abolishing the phenomenon of rebound pain. Salviz et al. [67] randomized patients undergoing outpatient arthroscopic rotator cuff repair to receive GA alone, or GA combined with either a single-injection or continuous interscalene block. Compared to the GA-only group, both RA groups had shorter PACU stays, were discharged home earlier, and had a longer interval to first analgesic use. Most notably, the incidence of severe pain (8–10/10 on a numerical rating scale) on the first postoperative day was only 15% in the continuous interscalene block group, compared to 78% and 40% in the single-injection and GA-only groups respectively. By the second postoperative day, the single-injection and GA-only groups had similar pain profiles, but the continuous catheter group continued to exhibit lower pain scores with only 10% reporting severe pain compared to 35% in the other two groups. A similar effect was reported for continuous versus single-injection popliteal sciatic PNB in patients undergoing ankle fracture surgery. The peak in pain score trajectory was both delayed and attenuated in the continuous catheter group, and at 48 and 72 h postoperatively, pain scores were similar in both groups. However, the overall value of outpatient PNB catheters is controversial [68]. Continuous RA techniques are technically more challenging to perform, have an inherent failure rate [69], are time and labor-intensive to manage, and consequently are likely to remain under-utilized in this setting [68].

Local anesthetic adjuncts in single-injection PNB

A more accessible alternative to continuous catheter techniques is the use of local anesthetic adjuncts to prolong the duration of single-injection PNBS. In a mouse model of sciatic nerve block with bupivacaine, the addition of perineural (but not intramuscular) dexamethasone prevented the appearance of a rebound hyperalgesic response to thermal stimulation [21]. Research indicates that perineural dexamethasone prevents bupivacaine-induced demyelination and Schwann cell degeneration [21], suggesting that any protective effect against rebound pain may be mediated by both anti-neurotoxic and anti-nociceptive mechanisms and effects. At present though, while it is well-established that dexamethasone (perineural more so than intravenous) [70] can prolong the analgesic benefit of PNB, there are no clinical studies specifically examining its impact on rebound pain per se.
Perineural buprenorphine is another local anesthetic adjunct used to prolong block duration, but again no studies have specifically investigated if it attenuates rebound pain compared to a control group. There is also a question of what constitutes an effective dose. In a retrospective cohort study describing their experience with a perineural combination of bupivacaine, clonidine, dexamethasone, and buprenorphine, Williams et al. [53] reported that a reduction in rebound pain after PNBs for total hip and knee arthroplasty was associated with > 300 μg buprenorphine but not lower doses.

Finally, although liposomal bupivacaine has been touted as an effective strategy to prolong the duration of analgesia (up to 72 h) with single-injection PNB [71], current evidence fails to support its routine use. Superior analgesia and opioid-sparing compared to conventional long-acting local anesthetics has not been demonstrated to date [72,73], and no studies have examined if it reduces the incidence and magnitude of rebound pain.

Multimodal analgesic regimens

As discussed above, PNB only blocks the transmission of nociceptive input to the spinal cord and higher centers. Peripheral sensitization and other physiological responses mediated by the humoral inflammatory response to surgery remain unaffected. Combining RA with systemic multimodal analgesia is therefore recommended for the potential additive or even synergistic benefits [74–76] in improving postoperative pain and related outcomes. Nevertheless, many studies investigating rebound pain after PNB do not routinely incorporate perioperative systemic multimodal analgesia, and outpatient surgery patients usually receive significantly less analgesic medication prior to discharge [13,29,77].

Although there is no direct evidence that a consistent and comprehensive multimodal analgesic regimen will reduce rebound pain, it should be prescribed on a routine basis as part of good clinical practice [3,11–13,29,67,78]. This should include a combination of acetaminophen, non-steroidal anti-inflammatory drugs /COX-2 inhibitors, and oral opioids [28,53,67,79–81], in the absence of any patient or surgical contraindications.

Preoperative education and counseling

As already mentioned, patients and caregivers should be clearly informed about both the advantages and limitations of RA. Day surgery patients should receive preoperative education on the finite duration of analgesia provided by PNBs, and depending on the surgical procedure, should specifically be warned to expect moderate/severe pain commensurate with the surgical procedure as the block wears off. They should be instructed to begin taking analgesic medication earlier rather than later, with an emphasis on the 15–20 min onset time for most oral analgesics versus the rapid offset of sensory block. A discussion of the expected interindividual variability [82] in block duration, pain thresholds, and response to analgesic therapy is also useful in assisting patients to self-titrate their medication. Supplementing verbal instructions with written or multimedia educational material will help improve compliance and lower perioperative anxiety and uncertainty [83].

Conclusion

Rebound pain is a transient perceptual phenomenon that occurs when the sensory blockade of RA resolves and unmasks ongoing nociceptive stimuli. Fortunately, in the majority of patients, it does not appear to significantly impact cumulative postoperative opioid consumption, quality of recovery, or patient satisfaction, and is not associated with longer-term sequelae such as PPSP. Rebound pain can, therefore, be viewed as a side-effect of RA but one that usually does not negate its favorable benefit-risk ratio. Nevertheless, rebound pain can cause acute distress and is an important consideration when formulating a perioperative management plan that involves RA, especially in outpatient surgery. Preoperative education is essential for setting appropriate patient expectations and coaching them on the importance of early preemptive initiation of systemic multimodal analgesia therapy. Prolonging the duration of action of PNB with continuous catheter techniques or with local anesthetic adjunctive medication may help alleviate rebound pain, although further research is required to confirm this.

Conflicts of Interest

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

Author Contributions

Felipe Muñoz-Leyva (Conceptualization; Data acquisition and analysis; Investigation; Methodology; Formal analysis; Writing – original draft; Writing – review & editing)
Javier Cubillos (Conceptualization; Validation; Visualization; Writing – review & editing)
Ki Jinn Chin (Conceptualization; Supervision; Formal analysis; Validation; Writing – review & editing)
References


Topical agents: a thoughtful choice for multimodal analgesia

Eunjoo Choi¹, Francis Sahngun Nahm¹,², Woong Ki Han¹, Pyung-Bok Lee¹,², Jihun Jo¹

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

For over a thousand years, various substances have been applied to the skin to treat pain. Some of these substances have active ingredients that we still use today. However, some have been discontinued due to their harmful effect, while others have been long forgotten. Recent concerns regarding the cardiovascular and renal risk from nonsteroidal anti-inflammatory drugs, and issues with opioids, have resulted in increasing demand and attention to non-systemic topical alternatives. There is increasing evidence of the efficacy and safety of topical agents in pain control. Topical analgesics are great alternatives for pain management and are an essential part of multimodal analgesia. This review aims to describe essential aspects of topical drugs that physicians should consider in their practice as part of multimodal analgesia. This review describes the mechanism of popular topical analgesics and also introduces the most recently released and experimental topical medications.

Keywords: Analgesia; Analgesics; Capsaicin; Cutaneous administration; Ketamine; Local anesthetics; Nonsteroidal anti-inflammatory agents; Opioids; Skin cream.

Introduction

One of the first concerns historically facing humanity would have been physical pain. It is no exaggeration to say that the history of medicine derived from humans trying to reduce pain. In modern times, these efforts to lessen pain are summed up by the term “multimodal analgesia,” which refers to a medical practice using diverse systemic medications with various mechanisms of actions [1,2] along with regional/peripheral block techniques [3].

For thousands of years, a variety of natural materials have been applied to the skin for treating pain. Some of these substances have active components that are still in use today. However, some substances that proved to be harmful have been discontinued, while others have long been forgotten.

Topical analgesics are great alternatives for pain management and an essential part of multimodal analgesia. Healthcare providers and pharmaceutical companies are now re-evaluating the effectiveness of potential analgesics and additional safety benefits from one of the oldest routes of drug administration: topical application. A survey reported that 27% of physicians prescribed compounded topical medications for pain relief, and 43% of patients responded favorably to topical agents with minimal side effects [4]. Topical drug administration has many potential benefits, especially in pain presentations that have localized and peripheral components (Table 1). The rationale of topical drugs is based on their ability to block or inhibit the pain pathway locally or peripherally, with minimum systemic uptake. Topical analgesic agents are easy to use and have obvious ben-
Table 1. Pros and Cons of Topical Drugs

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of use: convenient and painless</td>
<td>Localized skin irritation (e.g., erythema)</td>
</tr>
<tr>
<td>Direct access to the target sites</td>
<td>Intra and inter-individual variability of the skin can cause variable efficacy</td>
</tr>
<tr>
<td>Ease of dose titration and termination</td>
<td>Topical enzymatic activity may reduce the potency of the drugs</td>
</tr>
<tr>
<td>Avoid systemic adverse effects</td>
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effits, avoiding systemic adverse effects and drug-drug interactions, which can be observed in systemic drug administration. Hence, these agents are the preferred choice for elderly who take concomitant multidrug therapy for various diseases. In fact, the elderly are the main target population to benefit from topical agents; The American Geriatric Society recommended the use of topical agents for localized neuropathic and non-neuropathic pain [5]. Furthermore, topical agents usually do not require dose titration, as do many systemic agents. For these reasons, the use of topical agents is increasing. Since the United States Food and Drug Administration (FDA) approved topical analgesics, 8% capsaicin and 5% lidocaine patches (LP) to treat postherpetic neuralgia (PHN), many other drugs including ketamine cream, gabapentin gel, topical bacofer, and clonidine gel have been trialed.

Mechanisms of action for topical treatments include interactions with nociceptive neural networks in the outer layers of the skin through various inflammatory processes. Once applied to the skin, these substances must penetrate the stratum corneum, which can be a significant barrier. Substances that enhance this penetration have evolved in parallel with new topical drugs. Current topical medications with significant past histories that warrant discussion include nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetic agents, capsaicin, and ketamine. Topical routes of administration may increase due to the advent of new medications targeted to specific pain mechanisms and advances in drug penetration technology through the skin barrier. Furthermore, research on which patients will respond best to these methods of treatment is required.

This review aims to describe the key aspects of topical drugs that physicians should consider for their use as part of multimodal analgesia. The article discusses the differences between topical and transdermal drug delivery, the microstructure of the skin, and the mechanism of action of each medication. The latest topical medications are also described.

Transdermal vs. topical: the difference

The words "transdermal" and "topical" are often used interchangeably. However, it is necessary to distinguish between the two terms. The transdermal delivery of drugs is achieved by the percutaneous absorption of the substance, eventually reaching systemic therapeutic levels comparable with systemic administration. Therefore, transdermal drugs can be administered far from the area of pain and can cause adverse effects similar to systemic medication. Examples of transdermal agents are a sustained-release nicotine patch and long-acting fentanyl patch system. Despite the word ‘transdermal,’ the effect is primarily ‘systemic’ [6]. Transdermal delivery of medications serves as a reservoir within or adjacent to the skin, gradually releasing the substance into the systemic circulation leading to significant delays before reaching maximum plasma concentrations, making it a poor choice for sudden exacerbation of chronic pain or acute pain treatment [7]. Conversely, topical drugs target the underlying soft tissue and peripheral nerves at the application site. They exert their therapeutic action at the application site by penetrating the skin via passive diffusion [8]. Topical medications can accumulate at therapeutic concentrations within the local tissue to which they are applied while maintaining a low plasma concentration [8]. Due to the low systemic concentration, topical drugs do not cause adverse systemic reactions or interactions between drugs. Topical medications can potentially have similar efficacy to oral formulations on a locally applied site without the associated systemic side effects.

Absorption to the skin

The stratum corneum is the outermost layer of the epidermis, formed with dense, flattened keratinocytes (Fig. 1). This layer functions as a barrier to protect the underlying tissue from dehydration, infection, and chemical/mechanical stress. Topical medication must pass through the stratum corneum of the epidermis to show its effect [8]. After passing through this relatively impermeable barrier, the drugs can access the underlying cutaneous nociceptors: unmyelinated Aδ and C-fibers. The penetration of the stratum corneum is determined by the following essential parameters of the drug: oil/water partition coefficient, dimension, and superficial properties [9]. The stratum corneum is mostly hydrophobic, while the epidermis is predominantly aqueous. Therefore, an ideal topical drug should have a low molecular weight (<
500 Da) [10] and have both hydrophobic and hydrophilic characteristics to pass through the stratum corneum and aqueous epidermis [11].

The differences in the application site (e.g., the variation of the stratum corneum, skin integrity, and the density of appendages) can affect the absorption of topical drugs [12]. The integrity of the skin can be affected by pathological conditions and dehydration of the skin. Furthermore, the increased water content in the stratum corneum of 20–50% can cause swelling of the corneocytes, reducing the compactness of the layer and diffusion resistance [13]. The physical characteristics of the chemical contribute to the absorption of the topical agents. The more lipophilic the drug is, the more it is partitioned into the stratus corneum [14]. Also, the solubility of the molecule in its vehicle can affect the absorption and concentration of the drug in the skin. For a long time, numerous delivery agents have been designed to enhance the bioavailability and the absorbability of topical drugs. For example, lecithin organogels, pluronic gel, and pluronic lecithin organogel have been used [15, 16]. Moreover, patch or plaster formulations can be used, which provide additional benefit to traditional topical gels or creams because they can offer continuous and increased absorption [17].

Pain receptors in the skin

The keratinocytes, which constitute 90% of epidermis cells, are one of the main targets of topical analgesics. While keratinocytes are generally considered as non-excitable cells, they express various signaling molecules. Peripheral injuries induce keratinocytes and blood vessels in the dermis to produce excitatory factors, such as substance P, calcitonin gene-related peptide, and prostaglandin that bind to receptors on nociceptive fibers, resulting in depolarization. There is evidence that keratinocytes have both analgesic and algesic properties involving sensory transduction and modulation of epidermal sensory endings [18]. The analgesic property of keratinocytes express β-endorphins, which are released by the activation of endothelin-1 receptor B and cannabinoid 2 receptors, both expressed in the upper stratum of keratinocytes [19]. The algesic mechanism of keratinocytes involves the production of adenosine triphosphate and the calcitonin gene-related peptide β that are released by the activation of voltage-gated Na channels expressed on the keratinocytes [20].

The unmyelinated C and Aδ-fiber, which convey the feeling of pain, are stimulated by noxious stimuli of mechanical, chemical, and thermal inputs. Topical analgesics, such as capsaicin, ketamine, and lidocaine, act mainly on the free nerve endings of the unmyelinated C-fibers. The superficial stratum corneum contains free endings of horizontal distribution, also known as the sub-epidermal nerve net [21]. These endings originate from unmyelinated nerve fibers and are poor in axoplasmic organelles. Their main characteristic is the extensive neural network in the skin, distributed in the stratum corneum next to and inside the epidermis. This arrangement secures its efficacy in collecting the appropriate stimuli.

Topical agents

The oldest topical drugs may have been counterirritants to sup-
press the perception of pain. Counterirritants (e.g., menthol, camphor, peppermint oil, and garlic) have long been used throughout history. However, it was only recently that their molecular mechanism of action was revealed. Currently, various medications are applied topically (e.g., NSAIDs, local anesthetics, capsaicin, ketamine, and nitroglycerin) to reduce pain.

**NSAIDs**

NSAIDs are the most widely used commercially available topical agent and have diverse formulation. Among the topical agents, NSAIDs have the largest amount of clinical experience and accumulated evidence regarding their effect. Since the total systemic absorption from the topical application is only 3–5% of the oral administration, systemic toxicity from topical NSAIDs is consequently rare [22]. Previous studies have demonstrated that topical NSAIDs could reach sufficient therapeutic concentration; When applied topically, the concentration of ketoprofen was 30-fold higher in the adjacent cartilage than in the plasma. Furthermore, the $C_{\text{max}}$ values of ketoprofen of the intra-articular tissue were 6.8-fold higher in the topical route compared to oral administration [23]. Topical NSAIDs can be used in various painful conditions, including ophthalmic surgery, mucosal lesions, skin ulcers, strains/sprains, and venous cannulation [24–26]. Current guidelines in the United Kingdom recommend the use of topical NSAIDs ahead of oral administration for hand or knee osteoarthritis in consideration of the risk and benefits of pharmacological treatments [27].

**Local anesthetics**

Lidocaine inhibits the voltage-gated Na$^+$ channels and reduces the excitability of cutaneous sensory neurons. In the 1990s, a patch formulation of lidocaine 5% was developed and approved by the United States FDA for the treatment of PHN. Many guidelines recommend LP as first-line therapy for PHN [28,29]. Moreover, it has been increasingly used in other neuropathic conditions [30,31] and many pain-related conditions due to its ease of use and low systemic adverse effects [32,33]. Several studies have supported that LP provide adequate postoperative pain relief after various surgeries, including laparoscopic appendectomy [34], gynecological surgery with midline incision [35], radical prostatectomy [36], and endoscopic discectomy [37]. LP are 10 × 14 cm sized hydrogel adhesive patches containing 700 mg of lidocaine at a 5% concentration. A maximum of three patches per day is allowed on intact skin, with an on-off interval of 12 hours. On application, lidocaine is continuously released from the patch with ± 2% being absorbed systemically and more than 95% of the lidocaine remaining within the applied patch. Pharmacokinetic studies have demonstrated that the application of 5% LP resulted in systemic absorption of only 63 mg for a single 12-hour period application [38], with a peak plasma concentration of 0.13 μg/ml, which is only approximately 10% of the anti-arrhythmic dose [39]. This limited systemic absorption implies both minimal systemic side effects and minimal systemic analgesic effects, as intravenous lidocaine administration does possess an analgesic effect. Recent advances in patch technology have led to the development of 1.8% LP (ZTlido®, Scilex pharmaceuticals, Inc., USA) and a heat-activated topical lidocaine/tetracaine mixture patch (Synera®, Galen Ltd., UK). The former delivers the same amount of lidocaine as a conventional 5% LP and produces a similar analgesic effect, alongside the advantage of better skin attachment [40]. The latter enhances the delivery of local anesthetics through the skin triggered by local warming and can provide analgesia during superficial skin procedures such as venipuncture [41]. Recently a novel formulation of adhesive compounds for topical anesthetics, the film-forming system, has been developed to solve the problem of poor adherence in conventional patches. This system can also provide a metered-dose application. The film-forming system contains a mixture of the medication, film-forming polymer, and solvent system that, once applied, evaporates, and transforms to a thin film on the application site [42]. More effective topical lidocaine delivery technologies are anticipated in the near future.

**Capsaicin**

Substances for counter-irritation, which stimulate and subsequently desensitize nociceptive sensory neurons, have long been used. Although many of the substances in this group, such as camphor, menthol, and garlic, have a long history of general medical use, they have not been used as widely more recently. Capsaicin is considered to have the best evidence in pain treatment among the agents for counter-irritation. The effect of capsaicin on sensory fibers was first recognized in the early 19th century [43]. Topical capsaicin is currently used for alleviating PHN, painful diabetic polyneuropathy, chronic neck pain, HIV-peripheral neuropathy, post-traumatic, and postoperative chronic neuropathy [44]. This substance is an active ingredient in chili peppers belonging to the genus *Capsicum*. It is an irritant to mammals and causes a burning sensation in any tissue that comes into contact with it [45]. Capsaicin, as a member of the vanilloid family, binds to receptors and activates transient receptor potential vanilloid-1 (TRPV1), which opens transiently and initiates a depolarization mediated by an influx of Na$^+$ and Ca$^{2+}$. TRPV1 plays an important
role in pain transmission, especially pain during inflammation. It is expressed mainly in the primary sensory neurons with unmyelinated C-fibers. Various molecules and stimuli activate TRPV1, such as acidic or basic pH, high temperature above 42°C, transmembrane voltage, lipids, and protein kinases [46,47]. Once activated, TRPV1 leads to the perception of nociceptive stimuli. A previous study reported that TRPV1 undergoes up-regulation in certain disease processes, explaining the exacerbated pain associated with these conditions [48]. Topically applied capsaicin activates the TRPV1 channels and initiates a depolarization mediated by an influx of Na⁺ and Ca²⁺, followed by prolonged desensitization of the local pain nerves through TRPV1 expressing pain nerve fibers [49]. Capsaicin induces depolarization of the nociceptive free nerve endings, mainly the unmyelinated C-fibers with the generation of a resultant action potential that is propagated to the spinal cord and brain, ultimately perceived as a burning, warming sensation [50]. Additionally, capsaicin can lead to mitochondrial dysfunction by overloading the Ca²⁺ sequestration capabilities of mitochondria. Applying capsaicin in a higher concentration than that needed to activate the TRPV1 receptors leads to direct inhibition of the electron transport chain, eventually leading to mitochondrial destruction [51]. The half-life of capsaicin in the skin is estimated to be 24 hours [52]. When capsaicin is topically applied, it is hard to predict the resulting concentration due to much of it being stored in the stratum corneum. The systemic absorption of the capsaicin 8% patch has been previously reported. A one-hour exposure to capsaicin led to a systemic level of 1.75 ng/ml in a subject who had a treatment area of 924 cm², a value equivalent to dietary ingestion from chili peppers [53]. Ingesting 5 g of chili pepper contains approximately 27 mg of capsaicin, which results in an average Cmax of 2.5/ml [53]. Consequently, capsaicin 8% patch treatment is safe with low systemic absorption at a similar level to ingesting chili peppers in a standard meal. The major limitation of capsaicin use is its pungent effect on the area of application. This limitation may cause early discontinuation of the drug or reduced patient compliance. Distraction techniques appear to be efficient in alleviating the discomfort, and local cooling after capsaicin patch removal was found to be beneficial in relieving the burning sensation [54]. The most recent capsaicin approved by FDA was an 8% capsaicin patch, indicated for PHN. Low dose formulations in forms of patches, creams, and lotions containing 0.025–0.375% capsaicin for treating neuropathic or musculoskeletal pain are also available.

**Ketamine**

Ketamine, in sub-anesthetic doses, produces a systemic analgesic effect in chronic pain, mainly due to the blockade of N-methyl-D-aspartate (NMDA) receptors in the central nervous system and inhibition of central sensitization processes [55]. NMDA receptors are also located in peripheral sensory afferent nerve endings and can contribute to pain signaling [56]. Ketamine reduces the amplification of the responses to repeated stimuli. Topically applied ketamine may produce its peripheral anti-nociceptive effect by activating neuronal nitric oxide synthase [57]. Topical ketamine is available in a cream or gel formulation. There have been clinical trials on the effect of topical ketamine in postoperative pain [38] and complex regional pain syndrome [39]. The results of these studies were favorable for the use of ketamine without significant adverse effects. Unfortunately, there are no positive results from double-blind clinical trials for the topical analgesic effect in chronic neuropathic conditions. The major problem of topical ketamine is the risk of improper recreational use. As ketamine can be administered by many routes, there are concerns regarding the illegal recreational use of topical ketamine rectally, leading to undesirable effect [60,61]. Physicians should be cautious and aware of recreational use when prescribing topical ketamine.

**Nitroglycerin (NG)**

NG can be converted to nitric oxide (NO), an anti-inflammatory substance that is endogenously released by activated macrophages [62]. The generated NO can modulate the inflammatory process and produce an analgesic effect similar to the action of cholinergic drugs, via a mechanism directed at nociceptors. Cholinergic agents, such as acetylcholine, can induce analgesia by stimulating the release of NO. In a randomized, placebo-controlled trial, the effect of a 5 mg NG patch was evaluated for three days in relieving shoulder pain. After 48 hours, the NG group had significant pain reduction compared to the unchanged control group [62]. Another randomized, placebo-controlled study demonstrated that topical nitroglycerin was effective for reducing pain from chronic extensor tendinosis [63]. Compared to the placebo group, the topical nitroglycerin group showed significant pain reduction and increased strength of the wrist extensor.

**Other topical agents**

A great variety of other drugs are being developed or are currently used topically. Topical formulations containing various components, such as antidepressants, gabapentin, phenytoin, opioids, cannabinoids, and baclofen, are at various developmental stages [64]. An online survey reported that many clinicians use up
to 36 different agents for topical use [4]. However, no absolute standardization has been observed for the majority of compounding substances until now. Moreover, since there are only a few clinical trials available that examine topical agents, it is difficult to confirm the effectiveness of these drugs. Further clinical studies using standardized formulations are needed to demonstrate the effectiveness of these drugs for topical use.

Gabapentin is an anticonvulsant that inhibits the a2δ1 subunit of voltage-gated Ca\(^{2+}\) channels resulting in the reduction of neuropathic pain. Although there are only animal experiments, topical gabapentin gel at a 10% concentration showed similar outcomes to systemic gabapentin in reversing streptozotocin-induced vulvodynia and relieving allodynia in a streptozotocin-induced diabetes mellitus rat model [65]. Topical gabapentin alleviated severe pain from PHN and other neuropathic conditions [66]. A randomized controlled trial reported that topical 6% gabapentin was effective for reducing chronic kidney disease-associated pruritus [67]. Currently, a gel formulation containing gabapentin 6% and lidocaine 5% is commercially available in some countries.

Baclofen, a gamma-aminobutyric acid (GABA)B receptor agonist, reduces Ca\(^{2+}\) membrane conductance and increases K\(^{+}\) conductance to reduce pain [68]. In the peripheral nervous system, GABAB receptors are located in the cutaneous layers on keratinocytes and nerve endings. There have been some reports on the effectiveness of topical baclofen. Patients with vulvodynia treated with a topical baclofen 2% cream, reported significant pain reduction (> 50% improvement) compared to baseline [69]. A formula with a combination of ketamine 1.5%, baclofen 0.8%, and amitriptyline 3% showed promising results and improved symptoms of burning, tingling, and cramping pain in chemotherapy-induced neuropathy [70].

Phenytoin cream, a nonselective voltage-gated Na\(^{+}\) channel stabilizer, and GABAA receptor agonist showed promising results in allodynia reduction. Phenytoin 5% cream decreased allodynia for 8 hours in patients with diabetic neuropathy, while the 10% cream completely relieved symptoms for over 12 hours [71]. This agent was effective in reducing the pain at the episiotomy site [72] and reduced burning pain in patients with small fiber neuropathy in sarcoidosis [73].

Although there is much evidence supporting the use of systemic opioids for various painful conditions, topical opioids have been comparatively poorly investigated. The most common pain relief was achieved in patients with a pressure and malignant wound. However, patients with arterial leg ulcers did not benefit from topical opioids [74]. Preliminary results suggested that a combination of topical morphine and topical cannabinoid could have a synergistic effect [75].

Limitation of topical drugs

Although topical agents are related to a lower risk of systemic adverse effects than oral/intravenous medications, precautions are still required since the prevalence of hepatic and renal impairment is high in the elderly population. Reduction of renal and hepatic function, and the presence of various comorbidities controlled with multidrug therapy, leads to the use of topical drugs due to safety concerns with systemic drugs. Some topical agents have not been tested in patients with impaired renal or hepatic function, subsequently limiting their use for a broader patient population. The lack of evidence regarding topical medications in this population demands large-scaled safety trials. The use of topical agents has certain drawbacks. Topical analgesics should first be used on a small area of skin and thus not be used in conditions such as loss of skin integrity to minimize the risk of toxicity. Another significant limitation is the pungency of counterirritants such as capsaicin. It can lead to lowered patient compliance or other side effects when improperly applied. Additionally, off-label use of topical agents requires special precautions due to the high prevalence of renal and hepatic impairments in the elderly.

Also, the desired concentration of a drug remains a limitation despite the availability of various medications for topical use. It is necessary to improve the methods of drug delivery to penetrate the skin barrier efficiently while providing an effective therapeutic dose to reduce pain.

Future perspectives

Topical medications can be used alone or in combination with two or more agents. The combinations of different drug classes can be combined to create topical formulations that can target different mechanisms of action and possibly result in a synergistic analgesic effect. Previous studies have reported that a combination of topical morphine and topical cannabinoid can enhance the anti-allodynic effects while reducing the central effect of the opioids [75]. This result could lead to the development of newer combination agents. Further studies are needed to assess the efficacy and feasibility of topical compound formulations.

Besides, new agents should be trialed for use as topical formulations. For example, although it has not been used as a topical agent due to insufficient transdermal absorption, resiniferatoxin (RTX) could potentially be an efficacious topical drug. RTX is a potent capsaicin analog, which is extracted from the resin of the Euphorbia cactus [76]. RTX slows down depolarization and reduces Ca\(^{2+}\) influx into C-fibers [77]. RTX induces extremely prolonged channel opening and Ca\(^{2+}\) influx, resulting in cytotoxicity...
in TRPV1-positive pain fibers [78]. The sustained Ca\(^{2+}\) influx induced by RTX selectively destroys the peripheral nerve endings or the entire sensory neurons containing TRPV1 while sparing the motor, proprioceptive, and other somatosensory functions [79]. This selective neuro-ablation effect has been labeled as “molecular neurosurgery” [80]. There are promising results of RTX in the treatment of osteoarthritis [81]. However, permeation of RTX into the skin is inadequate, and research on enhancing its dermal absorbability is needed. If this research is successful, topical RTX could play an important role in topical analgesia.

**Conclusion**

Recent studies have broadened our understanding of the various mechanism through which topical medications result in pain relief. Due to the complex nature of pain, topical analgesia should be recruited as part of multimodal pain treatment. Enhancing the understanding of topical medications would be important to ensure optimal pain practice for patients requiring diverse, multimodal analgesic treatment options.

In summary, topical agents are a simple but effective method for treating pain and can play a crucial role in multimodal pain management. Further research is needed to elucidate the role and effectiveness of topical analgesics, especially when combined with other treatment modalities.

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**Conflicts of Interest**

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

**Author Contributions**

Eunjoo Choi (Writing – original draft)
Francis Sahngun Nahm (Conceptualization; Project administration; Writing – review & editing)
Woong Ki Han (Writing – review & editing)
Pyung-Bok Lee (Supervision)
Jihun Jo (Visualization)

**ORCID**

Eunjoo Choi, https://orcid.org/0000-0002-7002-3932
Francis Sahngun Nahm, https://orcid.org/0000-0002-5900-7851
Woong Ki Han, https://orcid.org/0000-0002-6894-9787
Pyung-Bok Lee, https://orcid.org/0000-0003-0325-3356
Jihun Jo, https://orcid.org/0000-0002-3590-0733

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A double-blind, placebo-controlled trial of a topical treatment
for chemotherapy-induced peripheral neuropathy: NCCTG trial
Paravertebral block, especially thoracic paravertebral block, is an effective regional anesthetic technique that can provide significant analgesia for numerous surgical procedures, including breast surgery, pulmonary surgery, and herniorrhaphy. The technique, although straightforward, is not devoid of potential adverse effects. Proper anatomic knowledge and adequate technique may help decrease the risk of these effects. In this brief discourse, we discuss the anatomy and technical aspects of paravertebral blocks and emphasize the importance of appropriate needle manipulation in order to minimize the risk of complications. We propose that, when using a landmark-based approach, limiting medial and lateral needle orientation and implementing caudal (rather than cephalad) needle redirection may provide an extra margin of safety when performing this technique. Likewise, recognizing a target that is not in close proximity to the neurovascular bundle when using ultrasound guidance may be beneficial.

Keywords: Anatomy; Paravertebral; Postoperative pain; Regional anesthesia; Safety; Truncal nerve block.

Introduction

The thoracic paravertebral space (PVS) is a wedge-shaped space, with its base facing the lateral sides of the vertebral bodies and intervertebral foramina, and the apex being continuous with the intercostal spaces. It is bound posteriorly by the superior costotransverse ligament (SCTL), anterolaterally by the pleura, medially by the vertebrae and intervertebral foramina, and superiorly and inferiorly by the ribs (Fig. 1). It is generally considered to end at L1 with no defined cranial border. Each segment of the PVS communicates superiorly and inferiorly over the rib head and neck and is sometimes compartmentalized into anterior and posterior sections by the endothoracic fascia. This space contains the branching spinal nerve, sympathetic nerve fibers, and intercostal vessels embedded in adipose tissue and is usually continuous over the thoracic levels. The orientation of the neurovascular bundle (NVB) changes from medial to lateral in the PVS, with the intercostal vessels and nerves arising anteromedially, but eventually lying directly beneath the rib between the internal and innermost intercostal muscles (Figs. 2 and 3).

Proper identification of the space has traditionally been accomplished with landmarks using a predetermined distance lateral to the spinous process (SP) and/or loss of resistance. In some cases, this landmark technique has also been performed in combination with nerve stimulation, seeking an intercostal muscle twitch from intercostal nerve stimulation. More recently, ultrasound-guided (USG) paravertebral block (PVB) has become...
popular. Most approaches typically require identification of the transverse process (TP), and subsequently the SCTL (Fig. 4). While the landmark technique requires contact with the TP, other approaches, such as the lateral intercostal technique, do not require contact with this osseous structure [1].

As an anatomic space, the PVS will accommodate local anesthetic that can spread into cephalad, caudal, intercostal (including the dorsal intercostal compartments), interpleural, epidural, and prevertebral spaces. Depending on the volume, it may stay at the level of injection or spread to additional intercostal spaces with a caudal preference [2]. Similarly, bilateral spread is more likely if a large volume of local anesthetic is injected at a single site, as opposed to multiple low-volume injections at several adjacent sites.
Injection in the PVS should be easy and without resistance, with the goal of generating unilateral sensory, motor, and sympathetic blockade, though the somatic and sympathetic blockade may be variable. Its rapid onset is generally attributed to the local anesthetic being deposited into a small compartment containing small-sized nerves without a substantial covering of fascia [3]. Successful PVB will result in loss of cold sensation at the associated dermatomes to which the block was applied.

Discussion

Although serious adverse effects associated with PVB are relatively rare, they can include, but are not limited to, pleural puncture, pneumothorax, vascular puncture, nerve injury (central and peripheral), organ damage, local anesthetic toxicity, reaction to adjunct medications, post-dural puncture headache, and aberrant spread of local anesthetic (central and peripheral) [1]. Block failure rate with a landmark-based technique has been estimated in the literature as 6% to 10% [4]; however, this figure may be much lower in the hands of experienced anesthesiologists. For example, at Mayo Clinic Florida our PVB block failure rate is less than 1% after performing more than 5000 blocks (unpublished raw data). The overall incidence of adverse effects is usually no more than 5%, with hypotension being the most common development (4.6%), followed by vascular puncture (3.8%), pleural puncture (1.1%), and pneumothorax (0.5%) [3–5]. Nevertheless, patients for whom PVB is considered should be carefully evaluated for applicability and risk stratification; rare and devastating adverse effects, including pulmonary hemorrhage and development of chronic pain and Brown-Séguard syndrome, have been reported [6,7]. Here we will review the technical details of the landmark-based and USG techniques and discuss the relevant safety points associated with each.

Landmark technique

With the patient in a seated position, the superior edge of the SP is identified at the desired level. The location of the TPs can differ depending on the desired vertebral level of blockade, and cadaveric analysis describes that thoracic TPs encountered during PVB placement tend to correlate with the spinous process of the vertebral body 1 level cephalad [8].

The needle insertion point is marked approximately 2.5 cm lateral from the midline. At this point, a 22-gauge Tuohy needle (B. Braun Medical, USA) is inserted perpendicular to the skin, with the goal of contacting the TP (Fig. 4). Distances from the midline can be variable, but a more lateral starting point may result in missing the TP, and a more medial orientation risks violation of the neuraxis. Likewise, relationships between the lateral point of insertion and the depth of the TP can be variable (3–5 cm), generally requiring deeper needle insertion in the cervical and lumbar areas, and shallower distances in the thoracic regions. In patients with difficult surface anatomy, ultrasound can be a useful adjunct to assess depth to this bony structure and distance from the midline [9].

Once the TP is contacted, generally at a depth of 2 to 5 cm in adults, the needle is withdrawn into the subcutaneous tissue, redirected in a caudal direction, and then slowly advanced with the purpose of entering the PVS at an approximate depth of 1.0 to 1.5 cm past the initial contact with the TP. The depth of the PVS has been estimated at 3 to 6 cm from the skin surface, and passage through the SCTL may be appreciated in the thoracic region as a loss of resistance or, if a blunt needle is being utilized, a small ‘pop’. If bony contact is not obtained at the above suggested needle depth, it is likely that the needle tip is between the TPs. The needle is then redirected in an arc cephalad and caudad until the TP is contacted. If the TP is still not contacted it is assumed the needle is too superficial. The needle is then advanced 1 cm deeper and the process repeated until the TP is contacted. Once the TP is contacted and the needle redirected caudad off the TP, we suggest that excessive caudal angulation of the needle (> 45 degrees) should be avoided. In our experience, this appears to be associated with an increased risk of failed nerve block and adverse effects.

Considerations to improve safety during landmark technique

In the thoracic region, a loss of resistance or a ‘pop’ is usually associated with traversing the SCTL, while in the lumbar region, this same phenomenon is not associated with the PVS and may be instead indicative of a violation of the psoas fascia. Loss of resistance when entering into the PVS can also be appreciated, but given its subjective nature, we suggest that using predetermined parameters (i.e., needle depth of no more than 1.0–1.5 cm past the original point of contact with the TP) can help avoid adverse effects. Using the TP as an initial contact location for PVB provides a good reference point prior to further needle manipulation, especially when considering the proximity of the NVB and pleura. As Fig. 5 shows, even with advancement of the needle just 1.5 cm past the point of contact with the TP, the needle tip can be in close proximity to the pleura (with either a cephalad or caudal redirection). While both caudal and cephalad redirections of the needle after initial contact with the TP have been advocated, it is our opinion that, when using a landmark-based approach, consistently employing a caudal needle redirection to the PVS and minimizing medial and lateral deviation will lead to fewer adverse effects.
as the following four situations demonstrate:

1. Cephalad redirection of the needle after contact with the TP. Once the TP is located (Fig. 6A-1 and 6B-1), and the needle redirected, cephalad, the NVB, pleura, and lung lie directly within the needle path and are at risk of violation (Fig. 6A-2 and 6B-2, 4, and 5).

2. Caudal redirection of the needle after contact with the TP. Placement of the needle tip on the TP with subsequent caudal redirection places the needle in a relatively avascular non-neural location and may be shielded by the TP (Fig. 6A-3 and 6B-3).

3. Medial redirection or contact with the lamina. If the initial needle placement is too medial on the TP, or on the lamina, subtle needle redirection can help provide a more accurate approximation of the bony anatomy. However, advancement towards the PVS should not be directed cephalad or medial as it approximates placement of a thoracic epidural, with the risk of neuraxial puncture (Fig. 6B-4). Alternatively, caudal redirection should again help limit neurovascular injury: if the needle tip is potentially on the lamina, caudal redirection helps take advantage of the natural protective angle of the thoracic vertebra. Consistent contact with bone may be due to continued contact with the lamina, necessitating reassessment of the initial insertion site.

4. Lateral redirection or contact with the rib. If the needle is initially placed on the lateral portion of the TP and directed cephalad and lateral, the NVB or pleura may be trespassed (Fig. 6B-5). However, directing the needle tip in a caudal direction will aid in bypassing the NVB. Likewise, if the rib is first contacted, cephalad redirection risks placing the needle in the NVB, pleura, or lung, while caudal redirection will identify the inferiorly located TP (i.e., more shallow bony contact as the TP is more superficial than the rib). The initial contact point should then be moved to the TP.
When an attempt to enter the PVS is performed as described, maintaining a caudal needle direction while observing the above parameters may considerably decrease risk of inadvertent pleural, vascular, or neural puncture, regardless of which structure is first contacted. Of note, the rates of vascular injury and pleural puncture quoted by Lonnqvist et al. [4] reflect a caudal-to-cephalad needle redirection during landmark technique. In contrast, with the use of a cephalad-to-caudal needle redirection technique at Mayo Clinic Florida, the rates of these two complications are less than 1% at that institution, respectively [unpublished raw data]. Additionally, excessive angulation of the needle during PVB placement should be avoided, as steep angulation can bypass critical bony structures, lead to inappropriate needle endpoints, and result in block failure or adverse events.

**Ultrasound-guided technique**

There are several USG techniques to the PVS that generally have a high success rate with few adverse effects. Ultrasound can be used to easily identify key landmarks and needle position. Care must be taken to properly visualize the entire needle, avoid neuraxial adverse effects, and appreciate the SCTL and anterior displacement of the pleura in the subset of USG techniques that require their identification. Theoretically, direct visualization of the needle should decrease risk of adverse effects, while simultaneously confirming proper local anesthetic placement with anterior displacement of the pleura.

Generally, the ultrasound probe is positioned in a transverse (Fig. 7A) or sagittal (Fig. 7B) orientation, though modifications to these approaches have been suggested [10]. The type of approach dictates which landmarks are identified. An in-depth analysis is described by Krediet and colleagues [10]. Here, we briefly list the salient characteristics of these approaches.

1. Transverse USG probe orientation. With the ultrasound probe oriented transversely, key anatomic landmarks vary depending on the approach to the rib [1], TP [11–14], and inferior articular process [9] being used; parietal pleura, visceral pleura, and internal intercostal membrane may also be seen. Most approaches aim to place the tip of the needle between the internal and innermost intercostal muscles with a lateral-to-medial needle pathway and are performed in plane, though an out-of-plane medial-to-lateral approach has also been described [10].

2. Sagittal probe orientation. With the ultrasound probe oriented in the sagittal plane, the rib can be used as a lateral limit for transverse probe movement, and the TP as a medial limit [14,15]. With this probe positioning, the PVS will be visualized immediately caudal and anterior to the TP. The needle trajectory has been classically described as caudal-cranial or caudal-lateral/cranial-medial when in plane, and caudal-cranial out of plane.

**Fig. 7.** Ultrasound views of paravertebral space (PVS). (A) Transverse ultrasound view of the PVS, (B) Sagittal ultrasound view of the PVS. EIM: external intercostal muscle, IIM: internal intercostal membrane, TP: transverse process, PSM: paraspinal muscle.

**Considerations to improve safety during ultrasound-guided technique**

Both cadaveric and in vivo studies have shown that USG approaches can result in adequate spread of injectate within the PVS [10]. Pleural displacement can be a reliable visual end point for successful deposition of local anesthetic. While the use of ultrasound guidance will result in the ability to directly visualize the advancement of the needle between the internal and innermost intercostal muscles with a lateral-to-medial needle pathway and are performed in plane, though an out-of-plane medial-to-lateral approach has also been described [10]. With proper identification of these vascular structures, the block needle can be manipulated in a fashion that
minimizes the risk of neural or vascular injury. Depending on the ultrasound approach being utilized, this needle movement may very well involve either a caudal-to-cranial (Fig. 8A) or anteromedial (Fig. 8B) redirection. Thus, when using ultrasound guidance, the direction of needle orientation becomes less important than the final endpoint of the needle as long as both needle tip and neurovascular structures are well identified. Under ultrasound guidance one should aim to manipulate the needle towards the caudal area of the PVB space and avoid approaching the cephalad area of the PVS, thus potentially minimizing the risk of needle contact with the NVB.

Ultrasound-guided versus landmark technique

While ultrasound imaging is an invaluable tool in various regional anesthesia techniques, evidence regarding superiority of this technique compared to the landmark-based approach in PVB is mixed. A retrospective review by Saran et al. [16] found no difference in block efficacy, pain scores, opioid use, or complications between the two techniques. In contrast, a prospective randomized controlled trial among breast surgery patients suggested greater PVB success for USG techniques [17]. Perhaps not surprisingly, USG lateral-to-medial approaches to the PVS have been associated with higher incidences of epidural spread, believed to be due to needle direction toward the neural foramina and neuraxis, as compared to the landmark technique [5]. Conversely, the landmark technique takes advantage of the greatest antero-posterior dimension of the PVS (i.e., medial vs. lateral location) and does not require medial-to-lateral or lateral-to-medial needle direction, thereby limiting the dangers associated with these trajectories. Regardless of theoretical or actual advantages of using ultrasound for Paravertebral blockade, anatomic knowledge is still the most important factor in maximizing block success and safety. Further studies comparing the two techniques are necessary; in some patient populations the landmark technique can still play an important role.

Conclusion

Paravertebral blockade is an excellent regional anesthetic technique for primary or adjunct anesthesia and analgesia. Appropriate patient selection, anatomic knowledge, and proper technique are essential to patient safety. In landmark techniques accessing the TP, redirecting the needle caudally after contacting the TP may improve the safety of this block. Among USG techniques, actively manipulating the needle to avoid the NVB may similarly improve safety.

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Conflicts of Interest

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

Author Contributions

Alberto E Ardon (Investigation; Writing–original draft; Writing–review & editing)
Justin Lee (Conceptualization; Investigation; Writing–original draft; Writing–review & editing)
Carlo D. Franco (Investigation; Methodology; Writing–review & editing)
Kevin T. Riutort (Investigation; Methodology; Writing–review & editing)
Roy A. Greengrass (Conceptualization; Investigation; Writing–original draft; Writing–review & editing)

ORCID

Alberto E Ardon, https://orcid.org/0000-0002-9860-5811
Justin Lee, https://orcid.org/0000-0002-7226-4000
Carlo D. Franco, https://orcid.org/0000-0002-6354-7447
Kevin T. Riutort, https://orcid.org/0000-0002-8631-7564
Roy A. Greengrass, https://orcid.org/0000-0001-9732-0286

References

Five-year follow-up to assess long-term sustainability of changing clinical practice regarding anesthesia and regional analgesia for lower extremity arthroplasty

Mallika Tamboli1,2, Jody C. Leng1,2, Oluwatobi O. Hunter2, Alex Kou1,2, Seshadri C. Mudumbai1,2, Stavros G. Memtsoudis3,4, Tessa L. Walters1,2, Gregory Milo Lochbaum1,2, Edward R. Mariano1,2

1Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, 2Anesthesiology and Perioperative Care Service, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, 3Department of Anesthesiology and Public Health, Weill Cornell Medical College, 4Department of Anesthesiology, Hospital for Special Surgery, New York, NY, USA

Background: Long-term and sustainable clinical practice changes in anesthesia procedures have not previously been reported. Therefore, we performed a 5-year audit following implementation of a clinical pathway change favoring spinal anesthesia for total knee arthroplasty (TKA). We similarly evaluated a parallel cohort of patients undergoing total hip arthroplasty (THA), who did not undergo a clinical pathway change, and studied utilization rates of continuous peripheral nerve block (CPNB).

Methods: We identified all primary unilateral TKA and THA cases completed from January 2013 through December 2018, thereby including clinical pathway change data from one-year pre-implementation to 5-years post-implementation. Our primary outcome was the overall application rate of spinal anesthesia. Secondary outcomes included CPNB utilization rate, 30-day postoperative complications, and resource utilization variables such as hospital readmission, emergency department visits, and blood transfusions.

Results: The sample included 1,859 cases, consisting of 1,250 TKAs and 609 THAs. During the initial year post-implementation, 174/221 (78.7%) TKAs received spinal anesthesia compared to 23/186 (12.4%) cases the year before implementation (P < 0.001). During the following 4-year period, 647/843 (77.2%) TKAs received spinal anesthesia (P = 0.532 vs. year 1). The number of THA cases receiving spinal anesthesia the year after implementation was 78/124 (62.9%), compared to 48/116 (41.4%) pre-implementation (P = 0.001); however, the rate decreased over the following 4-year period to 193/369 (52.3%) (P = 0.040 vs. year 1). CPNB use was high in both TKA and THA patient groups, and there were no differences in 30-day postoperative complications, hospital readmission, emergency department visits, or blood transfusions between patients who underwent spinal and general anesthesia in both TKA and THA groups.

Conclusions: A clinical pathway change promoting spinal anesthesia for TKA can be effectively implemented and sustained over a 5-year period.

Keywords: Analgesia; Change implementation; Clinical pathway; Hip arthroplasty; Knee arthroplasty; Nerve block; Quality improvement; Regional anesthesia; Spinal anesthesia.
Introduction

The International Consensus on Anesthesia-Related Outcomes after Surgery group published recommendations in 2019 advocating for neuraxial anesthesia as the anesthetic technique of choice for patients undergoing total hip and knee arthroplasty [1]. Implementing these recommendations will represent a significant practice change for many anesthesiology groups, especially in the United States where nationwide database studies show that neuraxial anesthesia continues to be underutilized [2,3].

Despite the wealth of research data generated to guide clinical care, translation of research evidence to clinical practice is often a long and tedious process [4]. The barriers to implementing change have been extensively studied, and are both intrinsic and extrinsic [5]. In December 2013, within the context of a Perioperative Surgical Home (PSH) model, we implemented a change in our clinical pathway for total knee arthroplasty (TKA), offering spinal anesthesia as the preferred intraoperative anesthetic technique [6]. We based this decision on ample evidence demonstrating positive outcomes associated with the use of this technique [7]. At the end of six months, our spinal anesthesia utilization rate increased to 63%, from a previous rate of 13% for the six months pre-implementation [6].

However, despite successful implementation of a clinical practice change, evidence suggests that most changes are not sustained [8]. For example, one-third of improvement projects are reportedly abandoned within one year in the United Kingdom’s National Health Service [8]. The long-term sustainability of clinical practice changes in anesthesiology has not previously been reported. Therefore, we designed this study as a 5-year audit to examine the sustainability of a clinical pathway change at our institution favoring spinal anesthesia for TKA, hypothesizing that the rate of spinal anesthesia utilization would not differ between the first year post-implementation and the subsequent 4-year period. As a comparison, we evaluated spinal anesthesia utilization for a parallel cohort of total hip arthroplasty (THA) patients in the same time frame, since the THA clinical pathway was not changed to specify a preferred anesthetic technique. We also examined the utilization of regional analgesia in the form of continuous peripheral nerve block (CPNB), as part of the multimodal analgesic protocol and other postoperative outcomes in the PSH database for both TKA and THA.

Materials and Methods

This study was conducted with Institutional Review Board approval (28958) and waiver for informed consent (Stanford, CA, USA), and Veterans Affairs (VA) Research Committee approval (MAR0004; Palo Alto, CA, USA), at a university-affiliated tertiary care VA hospital with an active total joint replacement program, and a PSH [9,10]. The PSH program at our institution, and the TKA clinical pathway were previously described [6,11], and perioperative outcomes for inpatients are tracked using a customized PSH database [9]. The PSH database is populated by attending anesthesiologists, and is based on bedside visits on postoperative day (POD) 1, and electronic medical record reviews at POD 30.

In December 2013, at our regular departmental staff meeting, the TKA clinical pathway was changed to designate spinal as the preferred option for intraoperative anesthesia [6]. At the time, the data favoring spinal were deemed stronger for TKA compared to THA [7], so no change was made to our THA clinical pathway. The TKA clinical pathway change was endorsed by the department head and administrative champion, with unanimous agreement by all staff anesthesiologists. All anesthesiologists were provided with education and suggested language in standard work format for patient counseling, regarding anesthetic options for their knee replacement surgery. Our PSH team monitored adherence to the protocol, and provided each anesthesiologist with his or her rates of spinal anesthesia utilization, feedback on effectiveness of preoperative counseling, and re-training on the standard work as needed [6].

Study Population

We identified all primary unilateral TKA and THA cases completed from January 2013 through December 2018 to include data on the clinical pathway change from 1 year pre-implementation to 5 years post-implementation. We excluded duplicate entries and all surgeries other than primary TKA or THA (e.g., same-day bilateral surgeries, unicompartmental arthroplasty, and surgeries related to infection, reimplantation, or hardware removal plus arthroplasty). We then divided the sample into separate knee and hip replacement groups for analysis.

Outcomes

Our primary outcome was the overall spinal anesthesia usage rate in patients undergoing TKA. The initial one-year post-implementation rate was compared to the rate during the subsequent 4 years. Spinal anesthesia utilization rates one-year before, and one-year after implementation of the TKA protocol change were also evaluated. Similar comparisons were conducted in a parallel cohort of THA patients.
A secondary outcome was CPNB utilization rates in both the TKA and THA groups (adductor canal for TKA [12], and fascia iliaca for THA [13]). Additional outcomes included comparisons of 30-day postoperative event variables, based on anesthetic type and collected in the PSH database. Variables related to resource utilization included hospital readmission, post-discharge emergency department visits, and blood transfusions. Complications included cardiovascular events (e.g., myocardial infarction, arrhythmia, or cardiac arrest), pulmonary events (e.g., respiratory failure requiring intubation), delirium, catheterization for urinary retention, acute renal failure, ileus, surgical site infection, and death.

Statistical Analysis

Statistical analysis was performed with NCSS Statistical Software (NCSS, LLC, USA), and IBM SPSS Statistics Version 23 (IBM Corp., USA). Normality of distribution was determined for all scale variables using the Kolmogorov-Smirnov test. Single comparisons of normally distributed data were performed with Student's t test, while the Mann-Whitney U test was used for continuous data in non-normal distributions. The Chi square test or Fisher's exact test (n < 5 in any field) was used for categorical data comparisons. A value of P < 0.05 was considered statistically significant.

Results

Our initial query retrieved 2,298 TKA and THA cases. After removing duplicate entries (n = 130), and all surgeries other than primary unilateral TKA or THA (n = 309), the final sample consisted of 1,859 cases, including 1,250 TKAs and 609 THAs. Nearly all patients in both groups were male. The median (10th–90th percentiles) age for TKA patients was 67 (56–76) years, compared to 66 (55–77) years for THA patients (P = 0.782). In both groups, the median (10th–90th percentiles) American Society of Anesthesiologists physical status was 3 (2–3) (P = 0.913).

Primary Outcome

During the initial year post-implementation, 174/221 (78.7%) TKA patients received spinal anesthesia, compared to 23/186 (12.4%) the year before implementation (P < 0.001). Over the subsequent 4-year period, 647/843 (77.2%) TKA patients received spinal anesthesia (P = 0.532 vs. year 1; Fig. 1). Fig. 1 further divides the spinal category into those patients who received spinal anesthesia alone, vs. combined spinal and general anesthesia. The spinal anesthesia utilization rate in patients undergoing TKA did not fall below 50% for any quarter over the 5 years after implementation (Fig. 1). The number of THA group patients receiving spinal anesthesia during the year after implementation was 78/124 (62.9%), compared to 48/116 (41.4%) during the year before implementation (P = 0.001). Over the subsequent 4-year period, the spinal anesthesia rate in THA patients decreased to 193/369 (52.3%) (P = 0.040 vs. year 1 post-implementation; P = 0.040 vs. 1-year pre-implementation; Fig. 1). Among patients who received general anesthesia alone, the failure rates for attempted spinal anesthesia were 5.1% (21/406), and 3.1% (9/290) for TKA and THA, respectively.

Secondary Outcomes

The CPNB utilization rates for TKA and THA patients are shown in Fig. 2. The CPNB use rate for TKA patients did not change after implementation of the spinal protocol: 183/186 (98.4%) in the one-year pre-implementation, vs. 1049/1064 (98.6%) 5-years post-implementation (P = 0.742). The CPNB use rate increased in THA patients from 72/116 (62.1%) one-year pre-implementation to 376/493 (76.3%) 5-years post-implementation (P = 0.002).

Postoperative outcomes within 30 days are shown in Table 1. Overall, there were few complications, and there were no differences in the incidence of complications or resource utilization between spinal and general anesthesia, for either TKA or THA.

Discussion

The results of this 5-year audit show that a clinical pathway change in intraoperative anesthetic technique for patients undergoing TKA can be implemented and sustained long-term. During the same period, the rate of spinal anesthesia for THA also increased even in the absence of an explicit protocol change suggesting a secondary gain, since the same surgeons and anesthesiologists care for both TKA and THA patients. However, the long-term rate of spinal anesthesia utilization for THA was not sustained to the same degree as it was for TKA, which supports the benefit of actively maintaining the updated TKA clinical pathway.

Sustaining a clinical practice change over a long period of time requires integration of the change into an organizational routine [14]. A protocol becomes routine when it is memorized and adapted into context, reflects collective values, and conforms to rules governing decision-making [14]. Even when they become routine, clinical pathways and protocols will require ongoing maintenance, review, and reinforcement. Understanding what motivates physicians may also be helpful [15]. Taking pride in providing the best evi-
Fig. 1. Intraoperative anesthetic technique rates from January 2013 through December 2018 by quarter. For illustration purposes only, the spinal anesthesia category has been further divided into spinal anesthesia alone (“Spinal Only”), and spinal and general anesthesia combined (“Spinal+ GA”). TKA: total knee arthroplasty, THA: total hip arthroplasty, GA: general anesthesia, Q1: January through March, Q3: July through September.

Fig. 2. Rate of CPNB utilization from January 2013 through December 2018 by quarter. CPNB: continuous peripheral nerve block, TKA: total knee arthroplasty, THA: total hip arthroplasty, GA: general anesthesia, Q1: January through March, Q3: July through September.
Table 1. Thirty-day Postoperative Outcomes Based on Anesthetic Technique

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<th>Knee Replacement (n = 1,250)</th>
<th>Hip Replacement (n = 609)</th>
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<td>General (n = 406)</td>
<td>Spinal (n = 844)</td>
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<td>Readmission to the hospital</td>
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<td>Surgical site infection</td>
<td>2 (0.5)</td>
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Values are presented as number (%).

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<td>Death</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

dence-based care or following international recommendations [1] is an example of an intrinsic motivation [15]. Extrinsic motivations may relate to payment, and there is now a national quality measure in the United States related to utilization of regional anesthesia for TKA [16].

When we made the deliberate change in the TKA clinical pathway to initially offer patients spinal anesthesia [6], the intent was not to achieve 100% adherence. Patients may not receive spinal anesthesia for a variety of reasons (e.g., anticoagulation or patient refusal). However, we believe that patients who have no contraindications should be offered the option, and provided with supportive evidence when it exists [1,7]. The Regional Anesthesiology and Acute Pain Medicine (RAAPM) Service reinforces the clinical pathways at our institution. The RAAPM team co-manages all orthopedic surgery patients from admission until discharge, and is solely responsible for analgesic medications and interventions [11]. On a daily basis, a RAAPM team member sends an email to the anesthesiology attending physicians and residents assigned to the intraoperative care of joint replacement patients the next day to notify them of the multimodal analgesic plan (e.g., preoperative oral non-opioid analgesics and nerve block), and provide the intraoperative protocol suggesting spinal anesthesia as the preferred technique for knee replacement patients [6,11]. These clinical pathway protocols are also located in a shared drive on the veterans affairs workgroup server for anesthesiology.

In 2019, we changed our THA protocol to also favor spinal anesthesia as the first choice, based on new recommendations [1]. Although there are specific differences between THA and TKA with regard to intraoperative management (e.g., patient positioning, use of a tourniquet, blood loss), evidence suggests that neuraxial anesthesia is associated with benefits, even when combined with general anesthesia [1]. The rate of CPNB utilization is consistently high for all joint replacement patients at our institution. We attribute this to our PSH model in which the RAAPM team directly co-manages orthopedic surgery patients, and is primarily responsible for all aspects of pain management. The increase in THA patient CPNB utilization triggered in 2015 was secondary to the hiring of a new orthopedic surgeon who was particularly supportive of peripheral regional analgesia. Our CPNB data demonstrate our system's ability to adapt and efficiently implement practice changes that quickly become 'hard-wired,' and can be sustained over time. Within one quarter, nearly all THA patients were receiving CPNB, and this rate has not wavered since implementation.

There were several limitations to our study. First, the study was retrospective in nature. Second, the reported data are dependent on complete and accurate documentation in the electronic medical record, and integration of clinical information into the PSH database. Outcomes that are not routinely included in the PSH database (e.g., quality of recovery, patient satisfaction) are not available for analysis. Third, this study is clearly underpowered to detect differences in major postoperative complications due to the extreme rarity of these events. Larger database studies are more appropriate for studying these outcomes [17]. Finally, this study was conducted at a single, tertiary-care, university-affiliated VA hospital with a male-dominated patient population and other unique characteristics [18,19]; therefore, the clinical results may not be generalizable to other clinical settings and populations. However, we have identified some of the factors within our practice that may have made it possible to sustain long-term change, and these may be applicable to other practice settings.

In summary, a major clinical pathway change in intraoperative anesthetic technique for TKA patients can be effectively implemented and sustained over a 5-year period in the context of a PSH. In addition, our experience shows an increase in spinal anesthesia usage
for THA patients in the same timeframe, suggesting a collateral benefit from the TKA clinical pathway change.

Acknowledgements

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Conflicts of Interest

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

Author Contributions

Mallika Tamboli (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing – original draft; Writing – review & editing)

Jody C. Leng (Conceptualization; Investigation; Methodology; Resources; Supervision; Writing – original draft; Writing – review & editing)

Oluwatobi O. Hunter (Conceptualization; Investigation; Writing – review & editing)

Alex Kou (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing – original draft; Writing – review & editing)

Seshadri C. Mudumbai (Conceptualization; Investigation; Methodology; Resources; Supervision; Validation; Writing – review & editing)

Stavros G. Memtsoudis (Conceptualization; Methodology; Validation; Writing – review & editing)

Tessa L. Walters (Conceptualization; Resources; Software; Writing – review & editing)

Gregory Milo Lochbaum (Conceptualization; Methodology; Supervision; Writing – review & editing)

Edward R. Mariano (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)

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Randomized, controlled trial comparing respiratory and analgesic effects of interscalene, anterior suprascapular, and posterior suprascapular nerve blocks for arthroscopic shoulder surgery

Yean Chin Lim, Zhao Kun Koo, Vivian. W. Ho, See Seong Chang, Shivani Manohara, Qian Jun Tong

Department of Anesthesia and Surgical Intensive Care, Changi General Hospital, Singapore

**Background:** Interscalene brachial plexus block (ISB) provides excellent analgesia for arthroscopic shoulder surgeries but is associated with adverse effects including hemidiaphragmatic paresis. We aimed to compare the respiratory effects, forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV1) between suprascapular nerve block (SSB) and ISB.

**Methods:** Sixty patients were recruited and randomized into ISB, anterior SSB, and posterior SSB groups. FVC, FEV1, and diaphragmatic excursion were evaluated at baseline and 30 minutes after intervention. Blocks were performed under ultrasound guidance with 15 ml of 0.5% ropivacaine. Pain scores were assessed at 1, 6, 12, and 24 hours postoperatively.

**Results:** The ISB group showed a reduced FVC of $31.2\% \pm 17.5\%$ (mean $\pm$ SD), while the anterior and posterior SSB groups had less reduction of $3.6\% \pm 18.6\%$ and $6.8\% \pm 6.5\%$, respectively ($P < 0.001$). The ISB group showed more reduction in diaphragmatic excursion than the anterior and posterior SSB groups (median [IQR]): $-85.7\% (-95.3\%$ to $-63.3\%)$ vs. $-1.8\% (-13.1\%$ to $2.3\%)$ and $-1.2\% (-8.8\%$ to $16.8\%)$, respectively ($P < 0.001$). The median pain scores (IQR) in the ISB and anterior SSB groups were lower than those in the posterior SSB group at 6 hours on movement: $0 (0–2)$, $1.8 (0–4.5)$ vs. $5 (2.5–8)$, respectively ($P = 0.002$). There was no significant difference in oxycodone consumption postoperatively.

**Conclusions:** Anterior SSB preserves lung function and has a comparable analgesic effect as ISB. Thus, it is recommended for arthroscopic shoulder surgeries, especially in patients who have reduced lung function.

**Keywords:** Analgesia; Interscalene block; Regional anesthesia; Respiratory function; Shoulder arthroscopy; Suprascapular block.

**Introduction**

Interscalene brachial plexus block (ISB) has been shown to provide excellent analgesia for shoulder surgery and has been the standard regional anesthesia technique used for decades. However, some studies have quoted up to 100% incidence of phrenic nerve palsy [1]. This results in hemidiaphragmatic paresis and approximately 25–30% reduction in pulmonary function [2]. For patients with limited respiratory reserves, such as the morbidly obese [3], patients with chronic obstructive lung disease (COPD) [4], and the elder-
ly, this reduction can result in symptomatic dyspnea or desaturation. While the opioid-sparing effects of regional anesthesia are most valuable to these groups of patients, they are least likely to tolerate the reduction in lung function caused by an ISB. In addition, ISB is also associated with other adverse effects such as Horner’s syndrome, hoarseness of voice, and dense motor blockade.

Suprascapular nerve block (SSB) has been proposed as an alternative to the ISB in providing analgesia for shoulder surgeries as it has a lower likelihood of causing phrenic nerve blockade [5]. The suprascapular nerve innervates approximately 60–70% of the shoulder joint. There are two approaches to performing the SSB; posteriorly, in the supraspinous fossa, and anteriorly, in the suprascapular fossa. There are concerns that local anesthetic deposited via the anterior approach may still spread to the phrenic nerve and result in some degree of impairment of lung function.

The primary aim of this study is to investigate the effect of ISB and SSB (anterior and posterior approaches) on pulmonary function, forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV1). Our secondary aim is to compare their analgesic efficacy (pain scores and opioid consumption) and other adverse effects.

Materials and Methods

This study was approved by the Institutional Ethics Board (SingHealth CIRB, reference 2017/2459) and registered on clinicaltrials.gov, NCT03277326. Written informed consent was obtained from 60 patients undergoing arthroscopic shoulder surgery.

Patients scheduled for elective arthroscopic shoulder surgery under general anesthesia, aged 21 years old and above, American Society of Anesthesiologist physical status classification 1 to 3 and body mass index 18–35 kg/m² were included in this study. We excluded patients who were unable to give consent, were on chronic opioid therapy, allergic to drugs used in the study, had pre-existing neurological deficits, had pre-existing lung disease (COPD, uncontrolled asthma), and had any contraindications for regional anesthesia such as coagulopathy.

The patients were randomly assigned to three groups using a computer-generated block randomization list with allocation concealment. The primary anesthesiologist and data collector were blinded. Due to the nature of the study, the investigator performing the block could not be blinded. Sham blocks were not performed for ethical reasons and to avoid risk of unnecessary harm to patients.

On the day of admission, prior to surgery, a baseline FVC and FEV1 were measured using a bedside spirometer (Vitalograph ALPHA™, USA) in a seated position. Patients were instructed on how to use the spirometer and average readings of three attempts were used for analysis. In addition, bilateral diaphragmatic excursion, in centimeters, was measured by ultrasound using the anterior subcostal view, below the subcostal margin in the mid-clavicular line [6], during a vital capacity breath, using a 2–5 Hz low frequency curvilinear probe (Sonosite Edge™, FUJIFILM Sonosite Inc., USA). Premedication of oral paracetamol 1 g was administered 30 min preoperatively. The block was performed by one of the study investigators, who are competent in all three block techniques. Intravenous access was obtained and sedation with midazolam (up to 3 mg) was administered as required. Standard monitors were applied and supplementary oxygen was provided during the block. ISB, anterior and posterior approaches to SSB were performed under real time ultrasound guidance, Sonosite Edge, USA. In each group, 15 ml of 0.5% ropivacaine (75 mg of ropivacaine) was used for the block.

The ISB and anterior SSB were performed with the patient in a supine position, with the head turned to the contralateral side. For ISB, an ultrasound scan was performed to identify the C5, C6, and C7 nerve roots between the scalene muscles (Fig. 1). Local anesthetic was deposited between the C5 and C6 nerve roots, within the interscalene groove. For anterior SSB, the nerve was traced as it diverged from the brachial plexus to lie under the omohyoid muscle in the suprascapular fossa [7] (Fig. 2). Local anesthetic was deposited lateral to the suprascapular nerve, under the omohyoid muscle. Posterior SSB was performed with the patient in the seated position and the supraspinous fossa was identified by ultrasonography (Fig. 3). Local anesthetic was deposited in the supraspinous fossa, beneath the superior transverse scapular ligament and supraspinatus muscle [8].

Block success was assessed 30 min after performing the block by assessing the degree of sensory and motor blockade. Sensory block was tested by applying an ice block over the cutaneous in-
nervation of the respective nerves: the deltoid area for the axillary nerve, back of scapular for the suprascapular nerve, the lateral palm for the median nerve, the lateral aspect of the forearm for the musculocutaneous nerve, the lateral aspect of the back of the hand for the radial nerve, and the little finger for the ulnar nerve. Motor innervation was tested by assessing the strength of these movements: arm abduction for the axillary nerve, internal rotation of the arm for the suprascapular nerve, thumb opposition for the median nerve, elbow flexion for the musculocutaneous, elbow extension for the radial nerve, and finger abduction for the ulna nerve. Pulmonary function tests as described earlier were repeated.

General anesthesia was induced with intravenous fentanyl (up to 2 μg/kg), propofol (1–3 mg/kg), and atracurium (0.5 mg/kg). An endotracheal tube was used to maintain the airway and anesthesia was maintained on an oxygen/air/volatile agent mixture. Intravenous morphine (up to 0.2 mg/kg) was administered intraoperatively for analgesia, as required. The total amount of intraoperative opioids used was recorded. Intravenous ondansetron was given at the end of surgery for anti-emesis.

In the recovery area, intravenous morphine (up to 0.2 mg/kg) was administered to achieve a pain score of less than 3 before discharge to the ward. Regular oral paracetamol 1 g every 6 hours and etoricoxib 120 mg once daily was prescribed for postoperative analgesia. Oxycodeone 5 mg every 6 hours, as required, was administered for breakthrough pain.

The primary endpoint was the degree of reduction from baseline pulmonary function after the block. Pain scores at rest and on movement were recorded at 1, 6, 12, and 24-hour periods, after surgery, using an 11-point numeric rating scale. Patients were assessed at 24 hours for total opioid (oxycodeone) consumption and any adverse effects (postoperative nausea and vomiting, sedation, Horner’s syndrome, and hoarseness of voice).

Statistical analysis

The sample size was based on the study by Auyong et al. [9] where lung function (mean vital capacity) was reduced by 38% (SD 18) in the ISB group and 18% in the anterior suprascapular group. We aimed to detect a difference of ≥ 18% between groups in terms of reduction in lung function. For the study to have a power of 80% and a two-tailed P value of 0.05, we required at least 17 patients per group. We recruited 20 patients per group to account for possible cases of drop-out/loss to follow-up.

Data were analyzed using SPSS for Windows (SPSS ver. 20. IBM Inc., USA). Categorical data are presented as percentage and frequency. Parametric numerical data are presented as mean and standard deviation, while non-parametric data are presented as median (interquartile range). Categorical outcomes were analyzed with Chi-square test or Fisher’s exact test. Numerical data were compared among the groups with one-way ANOVA and non-parametric data with the Kruskal–Wallis test. Bonferroni correction was used to adjust for multiple comparisons. A two-tailed P value of < 0.05 was considered statistically significant.

Results

The study was conducted from September 2017 to April 2018 in Changi General Hospital, Singapore. Sixty-eight patients were
assessed for eligibility to be recruited for the study, of which six patients were not eligible and two patients refused to participate. Finally, 60 patients provided written, informed consent to participate in this study and were randomized according to the study protocol. All patients received the intended intervention; follow-up was completed and data were analyzed. CONSORT diagram of patient recruitment is in Fig. 4. The baseline demographics are presented in Table 1. There were no statistically significant differences with respect to age, sex, and ASA classification.

Block success was assessed after 30 min; the results are presented in Table 2. All three groups had high success rates of blockade of the suprascapular nerve (90–100%). The majority of patients who received ISB also showed blockade of other nerves in the brachial plexus, except the ulnar nerve, which was blocked in a small proportion of patients. Some patients who received SSB also showed blockade of the axillary nerve, especially with the anterior approach. Patients who received posterior SSB did not have any blockade of the median, ulnar, radial, and musculocutaneous nerves.

The respiratory effects of the different blocks are reported in Table 3. There was a significant reduction in FVC, FEV1, and diaphragmatic excursion of the ipsilateral side in patients receiving ISB, compared to those receiving SSB. The ISB group had a reduction of FVC of mean ± SD, 31.2% ± 17.5% while the anterior and posterior SSB groups had significantly less reduction of FVC by 3.6% ± 18.6% and 6.8% ± 6.5%, respectively (P < 0.001). Similarly, the diaphragmatic excursion decreased more in the ISB group than in the anterior and posterior SSB groups (median [IQR]): −85.7% (−95.3% to −63.3%) vs. −1.8% (−13.1% to 2.3%) and −1.2% (−8.8% to 16.8%), respectively (P < 0.001).

The analgesic effects of the different blocks are presented in Table 4. Median pain scores (IQR) in ISB and anterior SSB groups were lower than those in the posterior SSB group at 6 hours on movement: 0 (0–2), 1.8 (0–4.5) vs. 5 (2.5–8), respectively (P = 0.002). At 12 hours, pain scores on movement were also higher in the posterior SSB group than in the ISB group: ISB 2 (0–5), anterior SSB 4 (2–6.8) vs posterior SSB 6 (3–7.5), respectively (P = 0.017).

There was no statistically significant difference in intraoperative opioid consumption between the groups. The posterior SSB group had a trend toward requiring increased levels of morphine in recovery but this was not statistically significant after Bonferroni’s correction. There was no statistically significant difference in 24-hour oxycodone consumption; 65% of patients in the ISB group required oxycodone in the first 24 hours compared to 45% in the anterior SSB group and 35% in the posterior SSB group.

There were no statistically significant differences in opioid-re-

---

Table 1. Baseline Demographics of Patients Receiving Interscalene, Anterior Suprascapular, and Posterior Suprascapular Block for Shoulder Arthroscopy

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>Interscalene (n = 20)</th>
<th>Anterior suprascapular (n = 20)</th>
<th>Posterior suprascapular (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>42.8 ± 17.2</td>
<td>40.3 ± 16.0</td>
<td>43.3 ± 15.5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>13 (65)</td>
<td>15 (75)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>F</td>
<td>7 (35)</td>
<td>5 (25)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3 ± 4.5</td>
<td>27.0 ± 3.8</td>
<td>24.0 ± 2.0</td>
</tr>
<tr>
<td>ASA PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (35)</td>
<td>7 (35)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>2</td>
<td>10 (50)</td>
<td>10 (50)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>3</td>
<td>3 (15)</td>
<td>3 (15)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Side of operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>15 (75)</td>
<td>7 (35)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Left</td>
<td>5 (25)</td>
<td>13 (65)</td>
<td>7 (35)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number of subjects (%). ASA PS: American Society of Anesthesiologists Physical Status.
Table 2. Sensory and Motor Blockade after Interscalene, Anterior Suprascapular, and Posterior Suprascapular Block at 30 Minutes

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Interscalene</th>
<th>Anterior suprascapular</th>
<th>Posterior suprascapular</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprascapular</td>
<td>18 (90)</td>
<td>18 (90)</td>
<td>19 (95)</td>
<td>0.804</td>
</tr>
<tr>
<td>Sensory</td>
<td>20 (100)</td>
<td>19 (95)</td>
<td>19 (95)</td>
<td>0.596</td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>19 (95)</td>
<td>15 (75)</td>
<td>6 (30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Motor</td>
<td>20 (100)</td>
<td>12 (60)</td>
<td>9 (45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>18 (90)</td>
<td>3 (15)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Motor</td>
<td>16 (80)</td>
<td>3 (15)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ulnar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>12 (60)</td>
<td>11 (55)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Motor</td>
<td>3 (15)</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Radial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>18 (90)</td>
<td>3 (15)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Motor</td>
<td>18 (90)</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>19 (95)</td>
<td>4 (20)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Motor</td>
<td>19 (95)</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as number of subjects (%).

Table 3. Effects of Interscalene, Anterior Suprascapular, and Posterior Suprascapular Block on Respiratory Function and Diaphragmatic Excursion

<table>
<thead>
<tr>
<th>Respiratory function</th>
<th>Interscalene</th>
<th>Anterior suprascapular</th>
<th>Posterior suprascapular</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of FVC (%)</td>
<td>31.2 ± 17.5</td>
<td>3.6 ± 18.6*</td>
<td>6.8 ± 6.5*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Reduction of FEV1 (%)</td>
<td>30.1 ± 14.3</td>
<td>7 ± 10.9*</td>
<td>5.3 ± 8.1*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in ipsilateral diaphragmatic excursion (%)</td>
<td>−85.7 (−95.3 to −63.3)</td>
<td>−1.8 (−13.1 to 2.3)*</td>
<td>−1.2 (−8.8 to 16.8)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in contralateral diaphragmatic excursion (%)</td>
<td>4.6 (−14.2 to 46.3)</td>
<td>−7.2 (−19.1 to 11.9)</td>
<td>−2.5 (−10.7 to 8.8)</td>
<td>0.293</td>
</tr>
</tbody>
</table>

Percentage change from baseline, values are presented as mean ± SD or median (IQR). *Significant compared to interscalene, P < 0.001 (post-hoc comparison with Bonferroni's adjustment). FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second.

Table 4. Analgesic Effects of Interscalene, Anterior Suprascapular, and Posterior Suprascapular Block

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Interscalene</th>
<th>Anterior suprascapular</th>
<th>Posterior suprascapular</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h, at rest</td>
<td>0 (0-0)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0.068</td>
</tr>
<tr>
<td>1 h, on movement</td>
<td>0 (0-0)</td>
<td>1.5 (0-2.8)*</td>
<td>1 (0-3)</td>
<td>0.013</td>
</tr>
<tr>
<td>6 h, at rest</td>
<td>0 (0-1.9)</td>
<td>0 (0-0)</td>
<td>0 (0-2.4)</td>
<td>0.256</td>
</tr>
<tr>
<td>6 h, on movement</td>
<td>0 (0-2)</td>
<td>1.8 (0-4.5)</td>
<td>5 (2.5-8)*</td>
<td>0.002</td>
</tr>
<tr>
<td>12 h, at rest</td>
<td>0 (0-2.8)</td>
<td>0 (0-2.8)</td>
<td>0 (0-2)</td>
<td>0.768</td>
</tr>
<tr>
<td>12 h, on movement</td>
<td>2 (0-5)</td>
<td>4 (2-6.8)</td>
<td>6 (3-7.5)*</td>
<td>0.017</td>
</tr>
<tr>
<td>24 h, at rest</td>
<td>3 (0-5.4)</td>
<td>0 (0-5)</td>
<td>0.8 (0-2.9)</td>
<td>0.280</td>
</tr>
<tr>
<td>24 h, on movement</td>
<td>5.5 (3.5-8)</td>
<td>5 (3-8)</td>
<td>5.3 (5-7.9)</td>
<td>0.865</td>
</tr>
<tr>
<td>Induction, Fentanyl (μg)</td>
<td>87.5 (75-100)</td>
<td>100 (81.3-100)</td>
<td>100 (75-100)</td>
<td>0.358</td>
</tr>
<tr>
<td>Intraoperative, Fentanyl (μg)</td>
<td>0.0 (0.0-18.8)</td>
<td>0.0 (0.0-25.0)</td>
<td>0.0 (0.0-50.0)</td>
<td>0.525</td>
</tr>
<tr>
<td>Intraoperative, Morphine (mg)</td>
<td>2.0 (0.0-4.0)</td>
<td>4.0 (0.0-5.0)</td>
<td>4.0 (2.0-6.0)</td>
<td>0.140</td>
</tr>
<tr>
<td>Recovery, Morphine (mg)</td>
<td>0.0 (0.0-0.0)</td>
<td>0.0 (0.0-0.0)</td>
<td>0.0 (0.0-4.0)</td>
<td>0.041*</td>
</tr>
<tr>
<td>Oxycodone consumption in first 24 h (mg)</td>
<td>5.0 (0.0-10.0)</td>
<td>0.0 (0.0-5.0)</td>
<td>0.0 (0.0-5.0)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

Values are presented as median (IQR). Post-hoc comparison with Bonferroni's adjustment: *P = 0.027 (compared to interscalene), †P = 0.003 (compared to interscalene), ‡P = 0.018 (compared to interscalene), §P = 0.030 (compared to anterior suprascapular), †P = 0.003 (compared to anterior suprascapular), ‡Post-hoc comparison with Bonferroni correction did not reveal any significant difference.
lated side effects such as sedation, nausea, and vomiting. None of the 60 patients were sedated. None of the patients in the ISB group had nausea and vomiting while two patients in the anterior SSB group had nausea, out of which one had vomiting, and two in the posterior SSB group had nausea and vomiting.

Regarding complications, the ISB group had one patient with hoarseness of voice and one patient with Horner’s syndrome. No patient complained of dyspnea or had desaturation. No patient had other block-related complications such as bleeding, hemoptoma, infection, or nerve injury.

**Discussion**

The results of our study showed that both approaches of SSB preserved lung function compared to the ISB, which resulted in a decrease in FVC, FEV1, and diaphragmatic excursion. The analgesic effect of the anterior SSB and ISB were superior to that provided by the posterior SSB. Two patients in the ISB group had adverse effects; one patient had Horner’s syndrome and another patient experienced hoarseness of voice.

ISB is considered the gold standard for peri-operative analgesia for shoulder surgeries. However, as the phrenic nerve lies close to the interscalene groove, ISB is associated with phrenic nerve paresis in up to 100% of cases [1], resulting in ipsilateral hemidiaphragmatic paresis. Though well tolerated in healthy patients, patients with decreased respiratory function may experience symptomatic dyspnea or hypoxia. Various methods to avoid this adverse effect, including low-volume [10] and extra-fascial injections [11], have been attempted with limited success. Blockade of the suprascapular nerve, alone or in combination with the axillary nerve, have been suggested as an alternative means of analgesia, which could minimize the risk of phrenic nerve paresis [12,13].

The SSB was first described by Wertheim and Rovenstein [14] in 1941 for chronic shoulder pain and performed in the suprascapular fossa. The ultrasound-guided SSB technique was subsequently described by Harmon and Hearty in 2007 [8]. In this study, we had referred to this technique as the posterior SSB. However, several studies had shown that the analgesic effects were inferior to those of an ISB [12,13,15]. Siegenthaler et al. [7] described a new technique of blocking the suprascapular nerve in the supraclavicular fossa, and we used this as the anterior SSB in our study.

There is a paucity of studies on SSB using the anterior approach. Auyong et al. [9] investigated the effect on lung function from continuous ISB, supraclavicular, and anterior SSB and found less reduction of lung function with the anterior SSB (18%) than with ISB (38%). Wiegel et al. [16] compared ISB with anterior SSB and showed that pain scores with SSB were not inferior to those with ISB. However, their study did not investigate the effect on lung function.

As posterior SSB is performed well away from the phrenic nerve, one would expect no reduction in lung function. Some studies have shown that supraclavicular brachial plexus block results in impairment of respiratory function, possibly due to retrograde spread of local anesthetics [17]. This could suggest that anterior SSB performed in the supraclavicular fossa may have similar effects on respiratory function.

On the contrary, we demonstrated that lung function (FVC and FEV1) was preserved in both the anterior and posterior SSB groups compared to in the ISB group, which showed a reduction in lung function by almost a third from the baseline. Similarly, ipsilateral diaphragmatic excursion was preserved in patients who received a suprascapular block but drastically reduced in the ISB group. A recent study by Ferre et al. [18] showed an incidence of hemidiaphragmatic paralysis of 40% in the anterior SSB group and 2% in the posterior SSB group. A possible explanation could be that in our study, we intentionally scanned as distally as possible to isolate the suprascapular nerve and inject the agent lateral to the nerve to minimize deposition of the local anesthetic near the rest of the brachial plexus or the phrenic nerve.

FVC and FEV1 were chosen as parameters easily reproducible using a bedside spirometer. Studies have shown that FEV1 is strongly and positively correlated with diaphragmatic function [19,20]. Urmeys study demonstrated a reduction of FVC by 27% ± 4.3% and FEV1 of 26.4% ± 6.8% after ISB; our results were similar [2].

We chose to use 15 ml of 0.5% ropivacaine as this was the standard volume used for a single-shot brachial plexus block in our institution. Although a small volume could have been used to achieve intraoperative analgesia, the effects of the block may wear off rapidly. Despite the volume used in this study, there was little evidence of retrograde spread of local anesthetic from the anterior SSB to the phrenic nerve and minimal effect on the other major nerves of the brachial plexus.

Concerning analgesic efficacy, we found no statistically significant differences in pain scores at 6, 12, and 24 hours postoperatively between the anterior SSB and ISB groups. Our results are congruent with those of Auyong’s recent study [21] comparing single-shot anterior SSB, supraclavicular, and interscalene blocks, which showed that anterior SSB provided non-inferior analgesia than interscalene and also preserved vital capacity. Similarly, Abdallah et al. [22] also found that the anterior SSB was not inferior to the ISB for postoperative pain control. However, the analgesic effects of posterior SSB are inferior to those of ISB, with high pain...
scores at 6 and 12 hours on movement. These results are similar to findings from other studies [12,13]. More patients in the ISB group than in the SSB group required postoperative oxycodone, although there was no statistically significant difference in first 24-hour oxycodone consumption. We postulate that this might be due to rebound pain associated with ISB. As the ISB is a very dense block, patients may experience severe pain when the block wears off [23]. This could be another advantage of the SSB block, where studies have shown that patients have a smoother transition and less rebound pain than with ISB [24].

As the axillary nerve contributes about 10% of innervation to the shoulder, some authors have suggested combining the SSB with an axillary block [12,13]. In our study, we found that many patients who received SSB also experienced blockade of the axillary nerve, especially in the anterior SSB group (up to 75%). This could be due to the retrograde spread of local anesthetic to the posterior division of the upper trunk, which gives rise to the axillary nerve [25]. In Hanna’s study [26], the branching pattern in the upper trunk included the suprascapular nerve, posterior division, and anterior division. The posterior division is more closely related to the suprascapular nerve rather than the anterior division. Thus, it may be unnecessary to perform an axillary block to supplement the anterior SSB.

A known disadvantage of an ISB is having an insensate limb, which may be distressing to some patients and can result in injury to the limb. We found that the SSB can be quite selective in blocking the suprascapular nerve and axillary nerve. Hence, performing an SSB will minimize the risk of developing an immobile and insensate limb. Other adverse effects associated with an ISB, such as Horner’s syndrome and hoarseness of voice, can also be avoided with an SSB.

While it is not currently routine practice, we should consider doing bedside spirometry for patients prior to performing an ISB. It would be advisable to avoid ISB in patients with compromised lung function who are unable to tolerate a further 30% reduction. In this study, none of the patients experienced dyspnea/desaturation since we excluded patients with obesity or pre-existing lung disease. The baseline spirometry values of all our patients were within the normal range.

As we wanted to avoid performing sham blocks, we were unable to blind our patients. However, the principal anesthesiologists and outcome assessors were blinded. Another limitation was that we performed single-shot blocks with 0.5% ropivacaine and the effect might have worn off by 24 hours. We tried to overcome this limitation by assessing outcomes at 1, 6, 12, and 24 hours. Our study did not capture long-term outcomes.

In conclusion, anterior SSB was found to better preserve pulmonary function than ISB and there were no statistically significant differences in their analgesic effects. In addition, anterior SSB also had fewer adverse effects, such as Horner’s syndrome, hoarseness of voice, and dense motor blockade, than ISB. Therefore, we recommend performing anterior SSB in patients undergoing arthroscopic shoulder surgery, especially in the patients at high risk of respiratory compromise.

Conflicts of Interest

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

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Author Contributions

Yean Chin Lim (Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing)
Zhao Kun Koo (Conceptualization; Investigation; Methodology; Project administration)
Vivian. W. Ho (Conceptualization; Investigation; Methodology; Project administration)
See Seong Chang (Conceptualization; Investigation; Methodology; Project administration)
Shivani Manohara (Methodology; Project administration)
Qian Jun Tong (Conceptualization; Investigation; Methodology; Writing – review & editing)

ORCID

Yean Chin Lim, https://orcid.org/0000-0003-3679-7173
Zhao Kun Koo, https://orcid.org/0000-0003-4409-9420
Vivian. W. Ho, https://orcid.org/0000-0003-3133-7493
See Seong Chang, https://orcid.org/0000-0002-3240-3707
Shivani Manohara, https://orcid.org/0000-0001-6735-7846
Qian Jun Tong, https://orcid.org/0000-0002-7718-5272

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The relative analgesic value of a femoral nerve block versus adductor canal block following total knee arthroplasty: a randomized, controlled, double-blinded study

Jeff C. Gadsden¹, Siddharth Sata¹, W. Michael. Bullock¹, Amanda H. Kumar¹, Stuart A. Grant¹, Joshua R. Dooley²

Department of Anesthesiology, ¹Duke University Medical Center, Duke University, Durham, ²University of North Carolina Medical Center, University of North Carolina, Chapel Hill, NC, USA

Background: Multiple comparative studies report that adductor canal blocks provide similar pain relief to femoral nerve blocks following total knee arthroplasty. However, adductor canal blockade fails to anesthetize several important femoral nerve branches that contribute to knee innervation. We sought to clarify this anatomic discrepancy by performing both blocks in sequence, using patients as their own controls. We hypothesized that patients would experience additional pain relief following a superimposed femoral nerve block, demonstrating that these techniques are not equivalent.

Methods: Sixteen patients received continuous adductor canal block before undergoing knee arthroplasty under general anesthesia. In the recovery room, patients reported their pain score on a numeric scale of 0–10. Once a patient reached a score of five or greater, he/she was randomized to receive an additional femoral nerve block using 2% chloroprocaine or saline sham, and pain scores recorded every 5 min for 30 min. Patients received opioid rescue as needed. Anesthesiologists performing and assessing block efficacy were blinded to group allocation.

Results: Patients randomized to chloroprocaine versus saline reported significantly improved median pain scores 30 min after the femoral block (2.0 vs. 5.5, P < 0.001). Patients receiving chloroprocaine also required significantly fewer morphine equivalents during the 30 min post-femoral block (1.0 vs. 4.5 mg, P = 0.032).

Conclusions: Adductor canal block is a useful technique for postoperative pain following total knee arthroplasty, but it does not provide equivalent analgesic efficacy to femoral nerve block. Future studies comparing efficacy between various block sites along the thigh are warranted.

Keywords: Acute pain; Adductor canal block; Femoral nerve block; Ropivacaine; Total knee arthroplasty; Ultrasound.

Introduction

Adductor canal block is a common analgesic intervention for postoperative pain control following total knee arthroplasty [1,2]. This block is typically performed by depositing local anesthetic anterolateral to the femoral artery at approximately the mid-thigh in a musculofascial space bounded by the sartorius, adductor longus and vastus medialis muscles. Local anesthetic deposited here anesthetizes the saphenous nerve and the nerve to vastus medialis [2]. Both of these small nerves contribute to sensory innervation of the
medial knee joint [3]. A principal advantage of the adductor canal block is the relative absence of quadriceps weakness that is almost universal with femoral nerve block [4]. This muscle-sparing quality has been shown to facilitate early ambulation and recovery [5–7], and studies of block use for total knee arthroplasty show that the adductor canal block has largely replaced the femoral nerve block as the regional analgesic modality of choice [1,8].

Multiple investigations have suggested that the analgesic effect of the adductor canal block is equivalent to femoral nerve block following total knee arthroplasty, both in reported pain scores and opioid consumption [9–13]. However, femoral nerve block differs from adductor canal block in the number and distribution of individual nerves blocked. Specifically, the adductor canal block does not anesthetize either the nerve to vastus intermedius or the nerve to vastus lateralis, both of which contribute substantially to the sensory innervation of the knee joint [3,14]. Given this anatomic disparity, the results of the comparative trials [9–13] showing equivalence are somewhat puzzling. We questioned whether comparative studies of femoral nerve block and adductor canal block in separate cohorts of patients represented the most precise method of quantifying the relative analgesic effect of these two block techniques. To test that hypothesis, we designed a prospective, randomized, controlled study to evaluate this question using both blocks in each patient. Our hypothesis was that following total knee arthroplasty, the superimposition of a femoral nerve block to an existing adductor canal block would significantly reduce postoperative pain within 30 min of the intervention. If pain scores did not change after the femoral nerve block, this would support the widely held contention that femoral nerve block and adductor canal block provide equivalent analgesic effect following total knee arthroplasty.

Materials and Methods

Approval for this prospective, randomized, blinded clinical trial was obtained by the Duke University Institutional Review Board (IRB number: PRO00067430). This study was registered on clinicaltrials.gov, identifier number NCT03395990, on December 18, 2017. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Eligibility criteria for the study were age 56–85, American Society of Anesthesiologists physical status I–III, BMI 18–40 kg/m² and undergoing elective primary total knee arthroplasty. Patients were excluded if they had an allergy to local anesthetic, a contraindication to either femoral nerve block or adductor canal block, had chronic opioid consumption (defined as the use of ≥ 30 mg morphine equivalents per day in the seven days preceding surgery), had an inability to understand English, or were unable to cooperate with the protocol. All enrolled patients signed a written informed consent. Our primary outcome was pain intensity on an 11-point Numeric Rating Scale (NRS-11) at 30 min following the block intervention. Secondary outcomes included opioid consumption in the post-anesthesia care unit (in morphine milliequivalents), the presence of quadriceps spasm at any time during the post-anesthesia care unit stay, and the reported location of any pain in the knee area before the block and at 30 min following the block intervention.

Sample size

We defined a significant reduction in pain intensity as three points on a NRS-11. This value was chosen deliberately as is both clinically meaningful and validated as a measure of effectiveness of pain therapy in this population [15,16]. Our hypothesis was that the reported pain intensity would be reduced by three points with a femoral block compared to sham at the 30-minute time point following the block. To power a t-test with an assumed decrease of three points on the NRS-11, a standard deviation of two points at 80% power and an alpha = 0.05, we calculated that 8 patients per group would be required.

Standard interventions

In the preoperative block area, all patients received oral multimodal analgesia consisting of acetaminophen 975 mg, celecoxib 400 mg, and pregabalin 75 mg. Patients were then sedated with midazolam 2 mg IV and fentanyl 50 μg IV before receiving two peripheral nerve blocks in the operative limb. The first was infiltration of 20 ml of 0.2% ropivacaine with 1 : 400,000 epinephrine between the popliteal artery and the capsule of the knee (iPACK) using a technique described by Sinha [17]. Following this, an adductor canal perineural catheter was placed. A high-frequency linear ultrasound transducer (FlexFocus 400, BK medical, USA) was placed on the anteromedial thigh at the midpoint between the inguinal crease and the proximal aspect of the patella. Following skin infiltration with 1% lidocaine, a 100 mm, 18 gauge Tuohy needle (Contiplex B, B.Braun, USA) was inserted in-plane from lateral to medial through the skin and vastus medialis muscle and advanced toward the femoral artery in the plane immediately deep to the sartorius muscle. When the needle tip was directly adjacent to the artery (at approximately the position of the saphenous nerve), a small aliquot (0.5–1 ml) of 0.2% ropivacaine was injected and the ultrasound screen observed for evidence of the bolus adjacent to the artery and saphenous nerve. Small adjust-
ments were made to the needle tip position to obtain this result. Ropivacaine 0.2% 15 ml was then administered through the needle as the primary block, to create a pocket of injectate for the catheter. A 19 gauge perineural catheter was then passed through the needle and the needle withdrawn. The catheter position was adjusted as required until a 1 ml bolus through the catheter demonstrated the spread of injectate on the anterolateral aspect of the artery, directly adjacent to the saphenous nerve. The catheter was then secured to the skin with octylcyanoacrylate surgical glue (Dermabond, Ethicon Inc., USA), Steri-Strip™ wound closures (3M, USA), and a sterile transparent adhesive dressing (Tegaderm™, 3M, USA). The patient was then taken to the operating room for surgery. Each patient received a total of 20 ml of 0.2% ropivacaine for the adductor canal block. The catheter was capped off, and no additional infusate was administered until all of the study interventions were completed in the post-anesthesia care unit. Block success was tested immediately prior to induction of anesthesia by evaluating pinprick sensation on the medial calf just proximal to the medial malleolus using a three-point scale (0 = no sensation; 1 = partial sensation; 2 = full sensation).

General anesthesia was performed in order to rapidly and easily assess the effect of the adductor canal block and study blocks in the post-anesthesia care unit as well as to reduce the potential bias from a neuraxial block. Anesthesia was induced with fentanyl 1 µg/kg IV, propofol 2.5 mg/kg IV, and rocuronium 0.6 mg/kg IV. A supraglottic airway was then placed and anesthesia maintained with sevoflurane in an oxygen/air mixture, titrated to a bispectral index of 40–60. Ketamine 0.5 mg/kg IV of ideal body weight (up to a 40 mg maximum) and dexamethasone 10 mg IV were administered before incision as a part of the routine multimodal analgesic regimen. Fentanyl 25 mg IV was administered as needed to maintain heart rate and blood pressure within 20% of baseline. A pneumatic tourniquet was used on the thigh in all cases. Following cementing of the implant, residual neuromuscular blockade was reversed with neostigmine and glycopyrrolate, and ventilation switched from controlled to spontaneous; fentanyl was thereafter titrated in 25 µg aliquots to maintain a respiratory rate of 12–16 breaths/min. At the conclusion of the surgical procedure, sevoflurane was discontinued and the supraglottic airway removed.

**Study interventions**

Upon arrival to post-anesthesia care unit, a blinded investigator asked patients to report their pain quality, location, and intensity on the NRS-11 every 5 min. Success of the previously placed adductor canal block was tested again by the absence of sensation to pinprick on the medial calf. The contralateral calf was also tested as a control. Once the patient’s pain intensity reached five or greater or at time = 30 min post-arrival in the post-anesthesia care unit (whichever came first), the femoral nerve block intervention was initiated. We chose a pain intensity trigger of five based on pilot data from our institution demonstrating that knee arthroplasty patients who received general anesthesia and our standard nerve blocks had a mean peak pain score in the recovery room of 6.2 ± 1.4 (NRS scale 0–10).

Patients were randomly allocated into two groups using computer-generated random numbers. The group allocation was concealed in sealed opaque envelopes that were opened by an unblinded investigator prior arrival to the post-anesthesia care unit. Group C patients received a postoperative single-injection femoral nerve block with 15 ml of 2% chloroprocaine, and Group S patients received a sham femoral nerve block with 15 ml of normal saline. The study solution was prepared by the unblinded investigator. Chloroprocaine was chosen as the study local anesthetic so any associated motor block of the quadriceps muscles would resolve quickly and not impair overall recovery and physical therapy.

The ultrasound-guided femoral nerve block was performed by a blinded investigator on the operative limb using a standard technique [4]. A total of 15 ml of the study solution was deposited immediately adjacent to the femoral nerve at the level of the inguinal crease. Following the block procedure, the blinded investigator repeated the pain assessment every 5 min for 30 min. Patients were permitted intravenous hydromorphone in the post-anesthesia care unit 0.2–0.4 mg every 8 min as needed to treat pain intensity greater than five. Sensory testing of the ipsilateral saphenous nerve was repeated at 30 min post-block.

The presence of quadriceps spasm, opioid use in the post-anesthesia care unit, and any opioid-related adverse effects were also recorded.

**Statistical methods**

Statistical analysis was performed with SPSS for Windows (Ver. 24.0, IBM Corp., USA). Categorical variables were reported as count and frequency while continuous variables were reported as either mean and standard deviation or median and interquartile range depending on their respective distribution. Due to the low sample size, either Wilcoxon sum rank test or Fishers exact test was used to test the differences between continuous and categorical variables, respectively. The alpha level was set at 0.05 for statistical significance.
Results

Eight patients were randomized to each group. Patient demographics and pre-intervention data are shown in Table 1 and Fig. 1 depicts the CONSORT flow diagram of patient progress through the study. There were no differences between groups in age, body mass index, laterality of procedure, intraoperative fentanyl use, or time from removal of the supraglottic airway to placement of block in post-anesthesia care unit. Height and weight were higher in the chloroprocaine group, possibly due to a higher proportion of males. The adductor canal blocks were all successful as demonstrated by the loss of sensation proximal to the medial malleolus prior to induction of general anesthesia as well as in the post-anesthesia care unit. Compared to those receiving sham block (sham group), the patients receiving femoral nerve block with chloroprocaine (chloroprocaine group) experienced a significantly re-

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<th>Table 1. Characteristics and Pre-intervention Data of Patients Receiving Chloroprocaine (Group C) or Sham (Group S) Femoral Block</th>
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<td>Time from removal of supraglottic airway device to the block in PACU (min)</td>
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Values are presented as number of patients or mean ± SD, number (%). BMI: body mass index, PACU: post-anesthesia care unit, NRS: numeric rating scale. *Presents statistical significance.

Fig. 1. CONSORT flow diagram.
duced overall pain intensity. Median pain intensity was similar at the time of block and at 5 min post-block, but the chloroprocaine group showed a significant improvement after 10 min, and this reduction in pain intensity continued until data collection stopped at 30 min, at which point median (IQR) pain intensity was 2.0 (1.5–2.8) vs. 5.5 (4.0–6.5) for the chloroprocaine and sham groups, respectively (Fig. 2).

Intravenous opioid consumption (median morphine milli-equivalent in mg [IQR]) during the post-anesthesia care unit stay was significantly lower in the chloroprocaine group (1.0 [0–2.25 mg]) versus the sham group (4.5 [2.5–6 mg], P = 0.032). Two patients (one in each group) were identified as having quadriceps spasm pre-block. The spasm was completely relieved by the femoral nerve block in the chloroprocaine group, but not by the sham block. Pre-block knee pain location was characterized by patients as either ‘top of knee/anterior’ (12 patients), ‘diffuse/all over’ (three patients), or ‘medial knee’ (one patient). The primary location of pain remained anterior or diffuse after the femoral nerve block in 14 patients but changed to ‘posterior’ for two patients in the chloroprocaine group.

Discussion

Our results confirm the hypothesis that femoral nerve block and adductor canal block do not provide an equivalent analgesic effect for patients undergoing total knee arthroplasty. In this randomized, double-blinded controlled experiment, we were able to demonstrate that patients who had a carefully conducted and tested adductor canal block were able to benefit by > 3 points on the NRS-11 when femoral nerve block with chloroprocaine was superimposed, a result that is both statistically significant and clinically meaningful.

These results validate what is known about the innervation of the knee. The adductor canal block is thought to provide an effect by anesthetizing the saphenous nerve and the nerve to vastus medialis [14,18]. Blockade of these two specific nerves is theoretically attractive, as the principal approaches to total knee arthroplasty involve accessing the joint space via a medial (parapatellar, subvastus or midvastus) arthrotomy [19]. In addition, some studies have shown that, depending on the degree of distal spread in the adductor canal, this technique may result in blockade of genicular branch of the obturator nerve, which may provide additional analgesia [14,20].

However, knee arthroplasty involves more than simply incising the joint capsule, and there are multiple sources of postoperative pain that are transmitted by various branches of the femoral nerve. For example, the osteotomies performed on both the tibia and femur as well as the impaction of joint prostheses onto the bone surfaces involve periosteum that is innervated by all of the distal branches of the femoral nerve, including the nerves to vastus intermedius and lateralis [21]. Patellar resurfacing involves periosteum innervated by branches from the nerve to vastus lateralis [22]. Postoperative inflammation and edema of periarticular soft tissues stimulate nociceptive afferents that are transmitted by all branches of the femoral nerve, in addition to the sciatic and obturator nerves. Finally, quadriceps muscle spasm is a known complication following total knee arthroplasty that is associated with severe pain and unlikely to be relieved solely by a targeted...
block of the nerve to vastus medialis [23].

The femoral nerve block, which for many years was the gold standard analgesic therapy for total knee arthroplasty, relieves pain through blockade of its three principal motor/articular branches (nerves to vastus medialis, intermedius, and lateralis) as well as the saphenous nerve, and the intermediate and medial cutaneous nerves of the thigh. The articular, osteal, musculofascial, and cutaneous structures of the knee joint are innervated by a complex combination of all of these (in addition to sciatic and obturator branches) [3], and the contention that blockade of just two branches is equivalent to blockade of every branch of the femoral nerve is anatomically questionable [3,24].

Our patients served as their own controls, eliminating inter-rater variability as a confounder. Comparing pain intensity between two groups can be challenging due to the subjective nature of pain, especially when extensive multimodal therapies are employed [25]. Our methodology permitted the patients to ‘anchor’ their pain intensity after receiving an effective adductor canal block, and immediately prior to the femoral nerve block, allowing a meaningful determination of the effect, if any, of the intervention. We clearly observed two distinct patterns of pain intensity: patients in the chloroprocaine group experienced a linear decrease in pain intensity over the subsequent 30 min, whereas the median pain score in the sham group remained virtually unchanged. This finding verifies our contention that there is a significant analgesic value to the femoral nerve block above and beyond that achieved with adductor canal block alone. The fact that pain scores in the sham group showed little change, while receiving significantly more opioids in post-anesthesia care unit, only strengthens our conclusion that femoral nerve block provides superior analgesia to adductor canal block after total knee arthroplasty.

Indeed, not all studies of adductor canal block show equivalence to femoral nerve block. Memtsoudis et al. [26] performed both adductor canal and femoral nerve blocks (one in each thigh) in 60 patients undergoing bilateral total knee arthroplasty. Although overall pain scores on the visual analogue scale were similar at all time points, at 24 h, a significant proportion of patients reported more pain in the limb that had received an adductor canal block compared to the limb that received a femoral nerve block (50.9% vs. 25.4%, P = 0.017). In addition, a Cochrane database review of 8 trials comparing adductor canal block versus sham block revealed no differences in postoperative pain intensity at rest or with movement [27]. Moreover, multiple studies have reported that while maximum voluntary isometric contraction force of the quadriceps is preserved with adductor canal block, there is no clinical difference in ambulation or rehabilitation outcomes between adductor canal block and femoral nerve block [10,13,28–30]. Finally, long-term outcomes may also differ depending on the block used: in a retrospective study of over 5,900 patients undergoing unilateral total knee arthroplasty, the use of adductor canal block (vs. femoral nerve block) was associated with 2.87 (95% CI: 1.00–8.26) increased odds of developing persistent postoperative pain, a finding that supports the notion that there is a difference in the overall quality of acute pain control each technique provides [31].

Our study has several limitations. Firstly, our blocks were performed at mid-thigh. There exists some controversy as to the optimal location on the thigh for adductor canal block (as well as the nomenclature) [9,14], but since this is the approach that most investigators report [10,32–34], we determined it was a valid model. Notwithstanding, our results should be interpreted with this specific anatomic location in mind, and we cannot be certain that femoral nerve block would be superior to an adductor canal block performed at a substantially more proximal location. Secondly, we employed a general anesthetic in order to quickly evaluate the effect of our intervention. While this avoided the confounding effect of a neuraxial block, it may limit the interpretation of our results in cases where a spinal anesthetic is used and the pain experience is potentially less abrupt. Thirdly, we used 2% chloroprocaine at the femoral nerve in order to produce a short-acting block and prevent any extended quadriceps motor weakness, since our practice is to have patients ambulate within 1 to 2 h of surgery. It is possible that the chloroprocaine produced a different sensory effect than would have a femoral block using 0.2% ropivacaine. Finally, we only investigated the relative pain intensity and opioid consumption, so we cannot comment on the effect of femoral nerve block versus adductor canal block on any other outcomes. Certainly, there are surgical and anesthetic imperatives to providing motor-sparing blocks in order to enhance and accelerate recovery. We are not advocating for an abandonment of the adductor canal block for total knee replacement in favor of femoral nerve block as there is clearly a central place for this motor-sparing block in modern knee arthroplasty practice, especially with an increasing number of outpatient knee replacement procedures being performed. Rather, our research question was whether these two techniques, in fact, provide the same analgesia under very controlled conditions. Despite what appears to be the prevailing trend in the literature, the answer seems to be that these blocks are quite different in terms of pain relief.

In conclusion, the femoral nerve block confers superior analgesia following total knee arthroplasty compared to adductor canal block. While the adductor canal block is motor-sparing, it also appears to be partially sensory-sparing, as confirmed by the anatomic facts as well as our results. Further research into the role of
femoral nerve block versus adductor canal block for populations at particularly high risk for prolonged pain and/or opioid use is indicated, as well as the comparative value of femoral nerve block with adductor canal block when performed at various locations along the thigh.

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Conflicts of Interest

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

Author Contributions

Jeff C. Gadsden (Conceptualization; Data curation; Methodology; Project administration; Writing – original draft; Writing – review & editing)
Siddharth Sata (Conceptualization; Investigation; Methodology; Project administration; Writing – review & editing)
W. Michael. Bullock (Project administration; Writing – review & editing)
Amanda H. Kumar (Writing – review & editing)
Stuart A. Grant (Investigation; Methodology; Project administration; Writing – review & editing)
Joshua R. Dooley (Investigation; Project administration; Writing – review & editing)

ORCID

Jeff C. Gadsden, https://orcid.org/0000-0003-3971-3879
Siddharth Sata, https://orcid.org/0000-0002-8630-1861
W. Michael. Bullock, https://orcid.org/0000-0002-8088-8390
Amanda H. Kumar, https://orcid.org/0000-0002-3571-0788
Stuart A. Grant, https://orcid.org/0000-0001-9214-5175
Joshua R. Dooley, https://orcid.org/0000-0002-4147-8233

References


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Regional nerve blocks are an integral part of multimodal analgesia and should be chosen based on their efficacy, convenience, and minimal side effects. Here, we compare the use of pectoral (PEC II) and serratus-intercostal fascial plane (SIFP) blocks in breast carcinoma cases undergoing modified radical mastectomy in terms of the postoperative analgesic efficacy and shoulder mobility.

Methods: The primary outcome of this prospective controlled study was to compare the postoperative static and dynamic pain scores, and the secondary outcome was to assess the shoulder pain, range of shoulder joint motion, and hemodynamic parameters. Sixty patients were randomly allocated to three groups and given general anesthesia. All patients received paracetamol, diclofenac, and rescue doses of tramadol based on the institute's acute pain service policy. No block was performed in group C (control), whereas groups P and S received PEC II and SIFP blocks, respectively, before surgical incision.

Results: The groups were comparable in terms of age, weight, height, and body mass index distribution. Dynamic pain relief was significantly better 12 and 24 h postoperatively in groups P (P = 0.034, P = 0.040 respectively) and S (P = 0.012 and P = 0.017, respectively) compared to group C. Shoulder pain relief and shoulder mobility were better in group S, while the hemodynamic parameters were more stable in group P.

Conclusions: Both SIFP and PEC blocks have comparable dynamic and static pain relief with better shoulder pain scores in patients receiving SIFP.

Keywords: Mastectomy; Modified radical mastectomy; Nerve block; Pectoralis muscle; Postoperative pain; Shoulder pain.
However, chronic pain develops most often in cases that undergo axillary dissection of lymph nodes with mastectomy known as modified radical mastectomy (MRM) [2,3]. Preventive analgesia through multimodal approaches ensures control of continuous neuronal firing, which eventually decreases the incidence of chronic pain, morbidity, and mortality [4]. This includes giving regional analgesia along with parenteral analgesics during the early postoperative period and gradually stepping down to oral medications [5]. It is important to understand the area of pain distribution before we plan a regional nerve block for MRM. The skin overlying the chest and lateral thorax is supplied by anterior and lateral divisions of the intercostal nerves. The axilla is supplied by T1 and T2 dermatome, which includes the intercostobrachial nerve, whereas the pectoral muscles are supplied by lateral and medial pectoral nerves (branches from the lateral and medial cord of the brachial plexus) [6]. While there are various regional analgesic techniques used for MRM, including epidurals, intercostal nerve block, and paravertebral block, the fascial plane blocks are relatively new. Fascial plane blocks are often preferred because they avoid interfering with the epidural space, give a comparatively longer duration of pain relief with a single shot, and can be performed in patients with deranged coagulation without adverse side effects [7]. Pectoral (PEC) I block anesthetizes the lateral and medial pectoral nerves. In contrast, PEC II anesthetizes the medi- and lateral pectoral nerves, the anterolateral branch of the intercostal nerve from T2-T8/9, and the nerve to the serratus anterior, also known as the long thoracic nerve. A serratus plane block (SPB), if performed above the serratus anterior muscle between the serratus anterior and latissimus dorsi (LD), anesthetizes the anterolateral branch of the intercostal nerves T2-T8/9, the nerve to the serratus anterior and thoracodorsal nerve. A SPB below the serratus anterior muscle, also known as a serratus-intercostal fascial plane (SIFP) block, anesthetizes the lateral and anterior cutaneous branches of the intercostal nerves T2-T8/9 [8–10]. Information on analgesic duration and efficacy, postoperative dynamic mobilization, ease of performance, and side effects are the main concerns when deciding which analgesic block technique to use for MRM. Hence, this study aimed to compare PEC II and SIFP blocks in cases undergoing MRM for postoperative analgesic efficacy and shoulder mobility.

Materials and Methods

This was a prospective randomized, controlled, parallel-group, interventional trial, following the criterion of the Consolidated Standards of Reporting Trials. Bias was rigorously eliminated using the double-blinding technique. After approval from the institutional ethics committee (IEC no: 2016-10-IP-89), the study was performed using patients that underwent MRM surgery between December 2016 and December 2018. The study is enrolled in the clinical trial registry (CTRI/2017/10/009965) and, the clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. The primary objective of the study was to compare and assess the static and dynamic pain scores among the various groups. The secondary objectives were to compare shoulder pain, range of motion, postoperative nausea and vomiting (PONV), and hemodynamic alterations before and after surgical incision among the groups.

Cases were enrolled after they had consented for the procedure but were blinded to the group allocation. Randomization of cases was done when they were planned for the surgical procedure using the chit method. This was done by a surgical resident who was part of our project using 60 chits in a box. In the operation theater, the performer was informed about the group allocation, and the block was performed accordingly. Follow-up of the cases in the postoperative period was done by a resident who was not the performer and hence was blinded to the group allocation. Patients who underwent MRM and were aged between 18 and 60 years, female, American Society of Anesthesiologists grade I/II, with body mass index (BMI) < 40 kg/m² were included. Pregnant patients, patients allergic to local anesthetics, planned for an additional simultaneous breast reconstruction using either autologous tissue or prosthesis, duration of surgery exceeding 3 h, patients who could not understand the clinical research and the questionnaire of study were excluded.

After a comprehensive pre-anesthetic evaluation was performed and informed consent was sought, the patients were advised about the numerical rating scale (NRS) with 0 as "no pain," 1–3 as "mild pain," 4–6 as "moderate pain," and 7–10 as "severe pain." Patients were kept nil per mouth for 6 h, given lorazepam 0.5 mg the night before and ranitidine 150 mg early on the morning of surgery.

In the operation theater, intravenous access was obtained on the forearm contralateral to the operative breast. Standard monitoring with an electrocardiogram, non-invasive blood pressure, oxygen saturation levels was applied. All of the cases were induced using 0.01 mg/kg midazolam, 2 µg/kg fentanyl, 1–2 mg/kg propofol and 0.1 mg/kg vecuronium. The cases were maintained using inhalational agent sevoflurane, oxygen, and air. After induction, the block was performed under full aseptic precautions before surgical incision, as it was presumed that there could be disruption of the fascial planes post-surgery. The arm on the same side as the operation was positioned at 90° abduction, and the area of the block was painted using betadine with alcohol. The ultrasono-
nography (USG) machine was prepared using a linear transducer (6–13 Hz), and the probe was covered with a sterile sheet. Intra-operatively, all patients received paracetamol 1 gm intravenously (i.v) before the start of the surgical incision and an injection of fentanyl 1 μg/kg/h till completion of surgery. As a part of the institute’s acute pain services protocol, all cases also received paracetamol 1 gm i.v every 6 h and diclofenac 75 mg i.v every 8 h from the intra-operative period till two days after surgery. Injection tramadol 1 mg/kg (maximum to three times a day) was used for rescue analgesia.

The patients were divided into three groups:

- **Group C (control):** received no block.
- **Group P (PEC II block):** Patients were given a PEC block (PEC II) single shot using a USG machine with local anesthetic 0.2% ropivacaine 30 ml (10 ml between the pectoralis major and minor +20 ml between the pectoralis minor and serratus anterior).
- **Group S (SIFP):** Patients were given a block with 0.2% ropivacaine 0.4 ml/kg single shot.

The surgical incision was started 10 min after the block to give adequate time for the block to act. An i.v injection of ondansetron 4 mg and dexamethasone 8 mg was given to all patients to address PONV. Cases were extubated after surgery and were assessed immediately postoperatively, as well as 12, 24, and 48 h for static and dynamic pain, shoulder pain, rescue analgesic requirements, or any side effects. Complete shoulder abduction was not allowed prior to 6 h post-surgery because of wound and drain issues.

### Block performance

**For the PEC II block:** The USG probe was initially kept longitudinally over the clavicle in the midclavicular line, behind which is the first rib. Moving the probe downwards in the third intercostal space showed the thoracoacromial artery. Here, between the pectoralis major and pectoralis minor, we deposited 10 ml of 0.2% ropivacaine (PEC I block). This block anesthetizes the medial and lateral pectoral nerves. Then, the probe was rotated toward the axilla by 45°. Moving the probe to the anterior axillary line, the attachment of the serratus anterior muscle just above the rib could be seen. Here, in the third intercostal space, we deposited 20 ml of 0.2% ropivacaine between the pectoralis minor and serratus anterior muscle.

**SIFP block (SPB below the serratus anterior muscle):** The USG probe was moved beyond the PEC II position to the fourth intercostal space, midaxillary line, and again rotated into a longitudinal position to visualize the thick belly of serratus anterior and intercostal muscles below it. The needle was inserted in-plane under real-time visualization to hit the fourth/fifth rib, and 0.4 ml/kg of 0.2% ropivacaine was deposited.

### Statistical analysis

The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables are presented as the mean ± SD, whereas ordinal variables (NRS score) are presented as the mean ± SD (median). Means were also used to describe the ordinal data along with median. A one-way analysis of variance was used to compare the means among the three independent groups. The Kruskal Wallis test was used followed by multiple comparisons (Bonferroni test) to compare the distribution of the NRS pain scores among the three study groups. A paired sample t-test was used to test the change in means between the pre to post observations. Fisher’s exact test was used to compare the proportions between the groups. A two-sided P value of < 0.05 was considered statistically significant. Statistical Package for Social Sciences, version 23 (SPSS-23, IBM, USA) was used for data analysis.

To compare the detected means of the differences (pre-post observations, i.e., between the immediate postoperative and 24 h time points) of the NRS pain score in the three study groups, with a minimum two-sided 95% CI and 90% power, with an assumed effect size between the treatment and control of 0.5, the estimated sample size for each of the three study groups came out to be 18 (total 54). Similarly, with a minimum two-sided 95% CI and 90% power, we required at least 18 individuals to detect the effect size of 0.82 between paired observations. The sample size was estimated using G Power, version 3.1.9.2 (Düsseldorf University, Germany).

### Results

Out of the 150 patients evaluated for participation in this study, 60 eligible patients were enrolled and randomized into three groups, C, S, and P, with 20 in each group (Fig. 1). One patient in group C, as well as two each in groups S and P, were excluded during the process of data collection because their surgical plan was changed intraoperatively (primary closure of the wound was not achievable; hence a LD flap was done for wound cover). Therefore, data were analyzed for 19 patients in the control group C and 18 patients in each of the intervention groups S and P.

The mean age, weight, height, and BMI of the patients were comparable among the three groups (P = 0.382, 0.921, 0.411, and 0.861, respectively; Table 1).

The NRS scores for static and dynamic pain were both significantly less 12 and 24 h postoperatively in groups P and S, as com-
pared to group C. However, they were comparable with each other (Table 2).

The patients in group S complained of significantly less shoulder pain 12 and 24 h after the procedure as compared to groups C and P (Table 2).

The first evaluation of complete shoulder abduction was assessed for each patient after 6 h due to wound and drain issues, followed by 12, 24, and 48 h (Fig. 2). The patients were compared between the study groups in terms of their range of abduction. The results showed that the study groups were significantly associated with a range of movements at 6 h (P = 0.003) and 12 h (P = 0.002). In group C, the highest number of patients belonged to the 45–90° range of abduction at all time points. In groups S and P, the highest number of patients belonged to the 135–180° range of abduction at all time points. The proportion of patients that achieved shoulder abduction between 135–180° was significantly higher in group S at 6 h (P = 0.027) and 12 h (P = 0.018) postoperatively as compared to group C. However, the range of shoulder abduction was statistically the same among the three groups at all other time points.

The hemodynamic response to incision, as elicited by a rise in heart rate and blood pressure 1 min after incision as compared to 1 min before incision, was insignificant in group P, while significant in the other two groups (Table 3).

Rescue analgesia (an injection of tramadol) was required in three patients in group C and two in group S. Three patients of group C and two of group S reported postoperative nausea without vomiting. Out of the former three, two received tramadol as rescue analgesia. No other side effects, such as sedation or hypotension, were observed in any patient.

**Discussion**

Our results demonstrate that patients given PEC II/SPB below
Table 2. Comparison of the Numerical Rating Scale for Static, Dynamic, and Shoulder Pain among the Three Groups Postoperatively

<table>
<thead>
<tr>
<th>Time points</th>
<th>Group C (n = 19)</th>
<th>Group S (n = 18)</th>
<th>Group P (n = 18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Static pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>1.4 ± 1.6 (2.0)</td>
<td>1.4 ± 1.6 (2.0)</td>
<td>1.3 ± 1.5 (0.5)</td>
<td>0.851</td>
</tr>
<tr>
<td>12 h†</td>
<td>3.3 ± 2.9 (2.0)</td>
<td>1.9 ± 1.1 (2.0)</td>
<td>1.7 ± 1.1 (2.0)</td>
<td>0.047</td>
</tr>
<tr>
<td>24 h‡</td>
<td>2.7 ± 2.8 (2.0)</td>
<td>1.0 ± 0.9 (1.0)</td>
<td>1.7 ± 0.9 (1.0)</td>
<td>0.022</td>
</tr>
<tr>
<td>48 h</td>
<td>1.0 ± 0.9 (0)</td>
<td>0.5 ± 0.7 (0)</td>
<td>0.8 ± 1.3 (0)</td>
<td>0.098</td>
</tr>
<tr>
<td>Dynamic pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>4.3 ± 2.3 (4.0)</td>
<td>3.1 ± 2.9 (2.8)</td>
<td>2.9 ± 2.7 (2.8)</td>
<td>0.124</td>
</tr>
<tr>
<td>12 h†</td>
<td>4.5 ± 2.4 (4.5)</td>
<td>2.9 ± 1.4 (3.0)</td>
<td>2.5 ± 1.4 (3.0)</td>
<td>0.037</td>
</tr>
<tr>
<td>24 h‡</td>
<td>3.8 ± 2.1 (4.0)</td>
<td>1.9 ± 1.2 (2.0)</td>
<td>1.8 ± 1.3 (2.0)</td>
<td>0.018</td>
</tr>
<tr>
<td>48 h</td>
<td>1.4 ± 1.4 (1.5)</td>
<td>1.3 ± 0.9 (1.0)</td>
<td>1.4 ± 1.8 (1.0)</td>
<td>0.877</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>1.0 ± 2.0 (0)</td>
<td>0.9 ± 1.3 (0)</td>
<td>0.9 ± 1.5 (0)</td>
<td>0.775</td>
</tr>
<tr>
<td>12 h‡</td>
<td>2.9 ± 2.7 (1)</td>
<td>1.4 ± 1.5 (1.0)</td>
<td>2.5 ± 2.5 (2.5)</td>
<td>0.018</td>
</tr>
<tr>
<td>24 h‡</td>
<td>2.0 ± 2.4 (0)</td>
<td>0.8 ± 0.7 (1.0)</td>
<td>2.1 ± 2.4 (2.0)</td>
<td>0.028</td>
</tr>
<tr>
<td>48 h</td>
<td>0.2 ± 0.4 (0)</td>
<td>0.1 ± 0.3 (0)</td>
<td>0.7 ± 1.5 (0)</td>
<td>0.154</td>
</tr>
</tbody>
</table>

Values are presented as the mean ± SD (median). The Kruskal Wallis test was used to compare the distributions followed by multiple comparisons (Bonferroni test). *Statistically significant difference between group C and S, †Statistically significant difference between group C and P, ‡Statistically significant difference between group S and P. A P value of < 0.05 was considered statistically significant.

Fig. 2. Shoulder abduction in different study groups at different post-operative time intervals (6, 12, 24 and 48 h) are presented. The graph depicts the number of patients (in percentage) and its 95% CI. Fisher's Exact test has been used to compare the percentage. Result showed that the study groups were significantly associated with range of movements at 6 h (P = 0.003) and 12 h (P = 0.002). In 135-180°, there was significant difference in Group S at 6 h (P = 0.027) and 12 h (P = 0.018) post-operatively as compared to Group C.

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the muscle (SIFP) had a significant and comparable decrease in static and dynamic pain in the postoperative period (intergroup P > 0.05 between groups P and S). However, pectoral pain was controlled better in group P (PEC II), and shoulder pain was significantly less in group S (intergroup P < 0.05 at 12 h). Static pain is described as pain at rest, whereas dynamic pain is defined as pain on deep breathing, coughing or movement [11].

The analgesic effects of SIFP or PEC blocks have been studied previously [9,10,12–15]. No study has directly compared the efficacy of these two blocks in terms of pectoral pain, shoulder or axillary pain, and shoulder mobility after MRM, which is important to promote early physiotherapy to avoid long-term complications like lymphedema, axillary web syndrome (AWS), or shoulder immobility [16]. There was a study protocol that proposed to include shoulder mobility as a parameter in their study, including chest blocks, but to date, no data has been made available [17].

The static and dynamic NRS in both groups P and S were significantly less (P < 0.05) at 12 and 24 h compared to group C. The duration of the SPB below the serratus anterior muscle as proposed by Blanco et al. was approximately 360 min. The longer duration seen in our study can be explained by the use of dexamethasone, which was given to relieve PONV [18,19].

The evaluation of shoulder pain included pain in and around the shoulder joint, including the muscles, joint, axilla (which forms the inferior part of the shoulder joint), anterior, and posterior axillary fold. During the early postoperative period, shoulder pain is caused by surgical positioning, muscular spasms, and axillary retraction or manipulation. Our study emphasizes better coverage of shoulder pain in the SIFP group. A cadaveric study by Daga et al. [20] showed the cranial spread of dye up to T2/3 when the drugs were deposited in the plane between the serratus anterior and intercostal muscles at the fourth/fifth intercostal space. Further studies on this are required because out of the total 30 ml of saline that was used for the plane separation, the dye was mixed only in the last 10 ml. The fascia between the serratus anterior and intercostal muscles is continuous from T1-T8, so it is unclear what stops the drug from reaching the T1 dermatome, which, along with T2, covers the axilla, anterior and posterior axillary fold, and upper third of the arm. Blanco also found better axillary analgesia after SPB below the serratus anterior muscle because the drug is deposited directly in the midaxillary line over the exit of the lateral cutaneous nerve, compared to the PEC II group where the drug gradually seeps and reaches the target. Hence, less pain around the shoulder in group S could be an indirect representation of better coverage of T1 and T2 dermatomes. This is important because it would ensure pain-free shoulder mobility leading to early and effective physiotherapy, which is a major concern in cases undergoing axillary lymph node clearance to limit joint mobility due to lymphedema, rotator cuff tendinitis, or disuse muscular contracture [21].

Hemodynamic parameters 1 min after the incision were better controlled in group P (PEC II). This could be explained by the direct and faster coverage of the anterior cutaneous branches of the intercostal nerves by the PEC II block as compared to the SIFP block. Although, Fajardo et al. [12], in his study on SIFP, reported controlled hemodynamic parameters on the surgical incision that did not require rescue opioid dose despite less time between the block and surgery. In the literature, dexamethasone has been shown to delay the onset of block action [18]. Therefore, if we had waited longer before the surgical incision, we potentially could have controlled the hemodynamic parameters in group S (SIFP) as well.

Postoperatively, both groups had comparable pain relief. This could be explained by the gradual spread of drugs to the anterior hemithorax in group S [8,13]. This is due to the anatomical continuity of the serratus-intercostal plane up to the mid-clavicular line anteriorly and the seeping of drugs from the external intercostals to the more intimate layers.

We checked shoulder mobility by asking the patient to abduct their arm once at 6, 12, 24, and 48 h postoperatively. Maximum abduction was observed in patients of group S followed by group P and later by group C. However, this was statistically significant only at 6 and 12 h (P = 0.003 and P = 0.002, respectively). This could be correlated to less axillary and shoulder pain in patients

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**Table 3. Change in the Hemodynamic Values between Pre- and Post-incision**

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Heart rate</th>
<th>Systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before incision</td>
<td>After incision</td>
</tr>
<tr>
<td>Group C (n = 19)</td>
<td>85.1 ± 14.2</td>
<td>91.3 ± 15.8</td>
</tr>
<tr>
<td>Group S (n = 18)</td>
<td>77.4 ± 12.6</td>
<td>88.1 ± 17.4</td>
</tr>
<tr>
<td>Group P (n = 18)</td>
<td>77.9 ± 18.1</td>
<td>81.9 ± 20.7</td>
</tr>
</tbody>
</table>

† A one-way analysis of variance was used. A P value of < 0.05 was considered statistically significant.

Values are presented as the mean ± SD. * A paired t-test was used.
that received the SIFP block. Better shoulder mobility in patients that received the PEC II block compared to controls has also been found by Khemka et al. [22]. AWS is a condition that develops two weeks after axillary dissection in about 48.3% of patients, the main etiology of which is the discontinuity of the lympho-venous channels and myofascial trigger points [23]. To avoid the incidence of such trigger zones, it is necessary to maintain good arm mobilization postoperatively. It is debated as to whether physiotherapy should be started early or late; however, pain-free arm movements help in the performance of exercises.

SIFP and PEC II blocks have their own set of advantages and disadvantages. For example, while the duration of analgesia is comparable between the procedures, SIFP is easier to perform due to the endpoint of the needle and the drugs being deposited in one place. In contrast, PEC II blocks require precise placement of the needle tip first between the pectoralis major and minor and then between the pectoralis minor and serratus anterior. Thoracic nerves are selectively more targeted in the SIFP block, and vascular injury is more common while performing the PEC II block due to its proximity to the thoracoacromial artery [8]. The USG machine will always be a limiting factor in performing the PEC II block, unlike the SIFP, which can be performed blindly [14]. This can be achieved through surface markings using the midaxillary line, fourth/fifth intercostal space, and depositing the drug above the rib. We chose to use the midaxillary line rather than the posterior axillary line because the serratus anterior muscle belly is the thickest there, and it would be challenging for the drug to reach the anterior cutaneous nerve of the intercostal muscle from the posterior axillary line [20]. Also, the lateral branch of the intercostal pierces and branches into the anterior and posterior division in the midaxillary line to lie between the serratus and external intercostal muscles, hence ensuring its good coverage at this point.

The benefits of blocking the nerve to the serratus anterior and thoracodorsal nerves, which are primarily motor nerves, using SPB above the serratus anterior/PEC II block, are unclear. Anesthetizing the nerve to the LD will be beneficial if reconstruction is done using LD flap, but otherwise, in a regular MRM with primary closure, it does not appear to be overly beneficial. This could be due to relief of the muscular spasms induced by surgical manipulation, which might decrease axillary pain postoperatively. The concerns regarding motor nerve paresis have been raised previously with SPB above the serratus anterior muscle. This block was abandoned at some centres as it was found to disrupt the axillary fascia and hinder the surgical performance of the surgeons, who faced difficulty in identifying the long thoracic and thoracodorsal nerves by nerve stimulation as they were anesthetized [13]. As such, there were concerns raised regarding the potential to damage these nerves.

There are several limitations to our study. Only a small number of cases were included in the current study, and the hemodynamic monitoring was only conducted for a brief period. Furthermore, the patients were not followed up in the long-term to assess the incidence of surgical or chronic pain and the range of shoulder movement. However, to our knowledge, this is the first study to compare the SIFP and PEC II blocks in terms of the postoperative analgesic efficacy and range of shoulder movement. This study also questions the need to block the nerve to the serratus anterior and thoracodorsal nerve using SPB above the serratus anterior/PEC II block when equal analgesia can be achieved using SIFP (SPB below the serratus anterior) block. Further studies should be conducted to compare the efficacy of PEC I + SPB, PEC II, SPB and modified PEC II to evaluate the incision response, intra- and postoperative pectoral and shoulder pain with a longer follow-up period to see the effect on post-mastectomy syndrome and shoulder mobility. Moreover, studies with additives or a continuous catheter to increase the duration of analgesia could be performed, along with studies that examine the impact of starting physiotherapy earlier or later.

In conclusion, both SIFP and PEC II blocks were found to provide comparable dynamic and static pain relief. Shoulder pain and, in particular, axillary pain was found to be better managed with SIFP. A greater range of shoulder movement was possible after SIFP block compared to PEC II. However, the long-term effects were not examined in the current study.

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Conflicts of Interest

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

Author Contributions

Ushkiran Kaur (Formal analysis; Writing – original draft)
Chetna Shamshey (Conceptualization; Data curation; Investigation; Methodology; Visualization; Writing – original draft)
Anil Agarwal (Conceptualization; Project administration; Supervision; Writing – review & editing)
Neel Prakash (Writing – review & editing)
Ramya Chakrapani Valiveru (Investigation; Methodology; Writing – review & editing)

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ing – review & editing
Prabhaker Mishra (Formal analysis; Software; Validation)

ORCID
Ushkiran Kaur, https://orcid.org/0000-0003-3534-5706
Chetna Shamshery, https://orcid.org/0000-0002-3994-8531
Anil Agarwal, https://orcid.org/0000-0002-5231-9609
Neel Prakash, https://orcid.org/0000-0002-2586-6412
Ramya Chakrapani Valiveru, https://orcid.org/0000-0002-3994-8531
Prabhaker Mishra, https://orcid.org/0000-0003-4769-9106

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Antiallodynic and anti-inflammatory effects of intrathecal R-PIA in a rat model of vincristine-induced peripheral neuropathy

Kyungmi Kim, Wonyeong Jeong, In Gu Jun, Jong Yeon Park

Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Studies investigating the correlation between spinal adenosine A1 receptors and vincristine-induced peripheral neuropathy (VIPN) are limited. This study explored the role of intrathecal N6-(2-phenylisopropyl)-adenosine R-(-)isomer (R-PIA) in the rat model of VIPN.

Methods: Vincristine (100 μg/kg) was intraperitoneally administered for 10 days (two 5-day cycles with a 2-day pause) and VIPN was induced in rats. Pain was assessed by evaluating mechanical hyperalgesia, mechanical dynamic allodynia, thermal hyperalgesia, cold allodynia, and mechanical static allodynia. Biochemically, tumor necrosis factor-alpha (TNF-α) level and myeloperoxidase (MPO) activity were measured in the tissue underneath the sciatic nerve.

Results: Vincristine administration resulted in the development of cold allodynia, mechanical hyperalgesia, thermal hyperalgesia, mechanical dynamic allodynia, and mechanical static allodynia. Intrathecally administered R-PIA (1.0 and 3.0 μg/10 μl) reversed vincristine-induced neuropathic pain (cold and mechanical static allodynia). The attenuating effect peaked 15 min after intrathecal administration of R-PIA after which it decreased until 180 min. However, pretreatment with 1,3-dipropyl-8-cyclopentylxanthine (DPCPX, 10 μg/10 μl) 15 min before intrathecal R-PIA administration significantly attenuated the antiallodynic effect of R-PIA. This antiallodynic effect of intrathecal R-PIA may be mediated through adenosine A1 receptors in the spinal cord. Intrathecally administered R-PIA also attenuated vincristine-induced increases in TNF-α level and MPO activity. However, pretreatment with intrathecal DPCPX significantly reversed this attenuation.

Conclusions: These results suggest that intrathecally administered R-PIA attenuates cold and mechanical static allodynia in a rat model of VIPN, partially due to its anti-inflammatory actions.

Keywords: Adenosine; DPCPX; Neuropathy; Receptor; R-PIA; Vincristine.
standard analgesics in humans; therefore, rodent models of VIPN have been developed to elucidate these pain mechanisms [3]. Pharmacological studies using these models have indicated that the mechanisms underlying allodynia and hyperalgesia after vincristine treatment are complex [4].

Adenosine is an endogenous purine compound, and it functions as an extracellular signaling molecule in the peripheral and central nervous systems [5]. Adenosine is locally released at tissue sites in response to ischemia, trauma, and interactions with specific receptors. There exists abundant experimental data demonstrating the role of adenosine in the modulation of nociceptive transmission at the spinal cord level [6]. To date, four types of adenosine receptors have been identified and cloned, namely A₁, A₂A, A₃, and A₅ [5]. It is known that the antiallodynic and motor dysfunction effects of adenosine are mediated through the activation of spinal A₁ and A₂ adenosine receptors, respectively [7]. Activation of the adenosine A₁ receptor has been shown to reduce allodynia in neuropathic pain animal models [7,8]. After spinal nerve ligation, intrathecal administration of adenosine A₁ receptor agonists, including the R-(-) isomer of N6-(2-phenylisopropyl)-adenosine (R-PIA), is known to exert an antiallodynic effect mediated by the spinal adenosine A₁ receptor system in rats [7,8]. Preconditioning with R-PIA has been shown to protect the brain and neuronal tissue against ischemic damage [9]. This protective mechanism, which is mediated via adenosine A₁ receptor activation, activates a cascade of intracellular pathways, including adenosine triphosphate-sensitive potassium channel opening [9].

However, studies investigating the correlation between spinal adenosine A₁ receptors and VIPN are limited. Therefore, the present study was designed to investigate the antinociceptive and anti-inflammatory effects of an intrathecally administered adenosine A₁ receptor agonist, R-PIA, in a rat model of VIPN.

Materials and Methods

Experimental animals

A total of 50 male Sprague-Dawley rats (200–250 g, Orient, Seoul, Korea) were used across all experiments. Animals were housed in groups of 2–3 rats per cage in a room maintained at 22 ± 0.5°C with an alternating 12 h light-dark cycle. Food and water were available ad libitum. The animals were allowed to adapt to the laboratory environment for at least 2 h before testing. Experiments were performed during the light phase of the cycle (10 am–5 pm). All animal procedures and study protocols were approved by the Institutional Animal Care and Use Committee of the Asan Institute of Life Sciences, Seoul, Korea (IACUC Number: 2010-13-155).

Drugs and chemicals

Vincristine, the adenosine A₁ receptor agonist R-PIA, and the adenosine A₂A receptor antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) were purchased from Sigma-Aldrich Inc., St. Louis, MO, USA. All drugs were dissolved in sterilized saline (0.9% sodium chloride solution).

Induction of peripheral neuropathy with vincristine

Vincristine sulfate (100 μg/kg/day) was intraperitoneally administered for a period of 10 days (two 5-day cycles with a 2-day pause in between) and peripheral neuropathy was induced [10]. Pain assessment and behavioral examination were conducted on days 0 (before vincristine administration), 14, and 28 (Fig. 1).

Behavioral examinations

Cold allodynia (acetone drop test)

Cold allodynia was measured using the acetone drop method at the hind paw as described by Choi et al. [11], with small modification. The rat was placed on top of a wire mesh grid, and access to the hind paws was allowed. Acetone (0.1 ml) was applied to the plantar surface of the left hind paw by using a pipette with polyethylene tube and the duration of paw withdrawal was recorded in seconds using a stopwatch. The minimum and maximum values were 0.1 s and 20 s, respectively. This was conducted three times, with an interval of 5 min between applications, and the total individual withdrawal durations were then calculated.

Mechanical hyperalgesia (pin-prick test)

Mechanical hyperalgesia of the paw was evaluated using the pin-prick test, as previously described by Erichsen and Blackburn-Munro [12]. The surface of the injured hind paw was touched with the point of a bent gauge needle (at a 90° angle to the syringe) at an intensity sufficient to produce a reflex withdrawal response. Paw withdrawal latency was then recorded in seconds using a stopwatch with a minimum value of 0.1 s.

Thermal hyperalgesia (hot plate test)

The thermal nociceptive threshold, employed as an index of thermal hyperalgesia, was assessed by the hot plate method, using a plate maintained at a temperature of 52.5 ± 1.0°C. The rat was placed on the hot plate, and the withdrawal latency with respect to licking of the hind paw was recorded in seconds. A cut-off time of 15 s was used [13].
Fig. 1. Diagrammatic representation of the experimental protocol. DPCPX: 1,3-dipropyl-8-cyclopentylxanthine = adenosine A1 receptor antagonist; R-PIA: N6-(2-phenylisopropyl)-adenosine R-(-)isomer = adenosine A1 receptor agonist.
Mechanical dynamic alldynia (paint brush test)

The ‘paint brush’ behavioral test is well-established for investigating dynamic responses to a mechanical stimulus. Normal rats never withdraw from a smooth paint brush, so a response to this stimulus is described as alldynia. The rat was placed in a cylinder with a wire mesh floor and a smooth paint brush was used to rub the plantar surface of the hind paw from the heel to the toes. This stimulus was applied five times, with intervals of 5 s, and the number of withdrawals was noted (between 0 and 5). The same procedure was repeated twice, with a gap of 5 min, and the number of withdrawals across the three tests was summed to obtain a single cumulative score of mechanical dynamic alldynia. The minimum and maximum values were 0 and 15, respectively [14].

Mechanical static alldynia (von Frey filament test)

For assessment of mechanical state alldynia, the rat was placed in an individual plastic cage with a wire mesh bottom. After 20 min, the mechanical threshold was measured by applying a series of eight calibrated von Frey filaments (0.4, 0.6, 1.0, 2.0, 4.0, 6.0, 8.0, and 15.0 g; Stoelting Co., USA) to the mid–plantar surface of the hind paw, ipsilateral to the nerve injury. This was conducted until a positive sign of pain behavior was elicited, at which point it was then held for 6 s. A brisk withdrawal or paw flinching was considered a positive response, in which case the next lower force filament was then applied. In the absence of such a response, the next greater force filament was then applied. In the absence of a response at 15.0 g of pressure, this cut-off value was assigned to the animal. The mechanical stimulus producing a 50% likelihood of withdrawal was determined using the up-down method [15].

Intrathecal administration of drugs

Drugs were injected in 10 µl volumes by a direct lumbar puncture method between the L5 and L6 vertebrae [16]. Briefly, rats were anesthetized with sevoflurane in oxygen delivered via a nose cone. The lumbar region was shaved and prepared with Betadine. The animal on a 50 ml syringe body. Then, animals were administered the test drug at the L5-6 interspace using a 0.5-inch 30-gauge needle (Becton-Dickinson, USA) connected to a Hamilton syringe (Microliter™ #702, Hamilton Co., USA). The Hamilton syringe was filled with 10–20 µl of the test drug. The needle plunger was then slowly pushed over a 30 s period, delivering a volume of 10 µl, and the needle was immediately removed. The exact subarachnoid positioning of the tip of the needle was monitored using a tail- or paw-flick test [16]. Then, the animals recovered in their home cage before behavioral testing was conducted. All pain treatment groups and drugs were tested in a randomized order. The experimenters were blind to the drug treatment groups.

Behavioral examinations on the 28th day (cold and mechanical static alldynia)

On the 28th day, after behavioral examination (cold allodynia, mechanical hyperalgesia, thermal hyperalgesia, mechanical dynamic alldynia, and mechanical static alldynia), the antinociceptive and anti-inflammatory effects of intrathecal R-PIA were estimated as follows. A pretreatment dose of saline (10 µl) or DP-CPX (10 µg/10 µl) was intrathecally administered 15 min before intrathecal administration of R-PIA (0.3, 1.0, and 3.0 µg/10 µl). Measurements of cold and mechanical static alldynia were performed 15, 30, 45, 60, 90, 120, and 180 min after intrathecal R-PIA administration. Thirty minutes after the final measurements of cold and mechanical static alldynia (i.e., at 210 min), the animals were sacrificed. The sciatic nerve was then obtained, and biochemical estimations were conducted (Fig. 1). The doses of R-PIA and DPCPX administered in this study were chosen based on previous in vivo study involving rat models of neuropathic pain [17].

Biochemical estimations

Estimation of tumor necrosis factor-alpha level

After euthanasia, sciatic nerve samples were utilized for the determination of the tumor necrosis factor-alpha (TNF-α) level. TNF-α levels (sensitivity: 25 pg/ml) were determined using a rat TNF-α ELISA kit (R&D Systems, Inc., USA), following the manufacturer’s instructions. Testing of sciatic nerve homogenate samples was performed in duplicate. Recombinant anti-rat TNF-α was used to generate a standard curve (range: 0–20,000 pg/ml) as per the diagnostic kit. Absorbance was determined spectrophotometrically at 450 nm. The results were expressed as pg of TNF-α per mg of total protein in the supernatant.

Estimation of myeloperoxidase activity

Myeloperoxidase (MPO) activity was measured using a method described by Jain, Jaggi, and Singh [13]. After euthanasia, the sciatic nerve was obtained, and the nerve was minced and homogenized using a tissue homogenizer in an ice-cold potassium phosphate buffer (pH 7.4). The prepared homogenate was centrifuged at 5000 g for 10 min at 4°C. MPO activity in the supernatant was determined spectrophotometrically at 460 nm in the presence of hydrogen peroxide and 3,3,5,5-tetramethylbenzidine. The measured MPO values were expressed as MPO units (U)/mg of protein.
Experimental protocol

Eight groups were involved in the present study (Fig. 1).

**Group I: normal control animals (n = 7)**

The rats were subjected to no treatment and kept for 14 days. Behavioral tests were conducted on days 0, 7, 14, and 28. On the 28th day, after behavioral testing (cold and mechanical static allodynia), the animals were sacrificed. The sciatic nerve was then obtained and biochemical estimations were conducted.

**Group II: vincristine-treated control animals (n = 7)**

After induction of VIPN, behavioral examinations were conducted on days 0 (before treatment), 14, and 28. On the 28th day, a 10 μl pretreatment dose of saline was intrathecally administered 15 min before intrathecal administration of 10 μl saline. Measurements of cold and mechanical static allodynia were performed 15, 30, 45, 60, 90, 120, and 180 min after the intrathecal doses of saline. Thirty min after the final measurements of cold and mechanical static allodynia (i.e., at 210 min), the animals were sacrificed. The sciatic nerve was then obtained and biochemical estimations were conducted.

Groups III, IV, and V: R-PIA-administered (0.3 μg/10 μl, 1.0 μg/10 μl, and 3.0 μg/10 μl, intrathecal) vincristine-treated animals (n = 6 /each group)

After induction of VIPN, same behavioral examinations were conducted. On the 28th day, a 10 μl pretreatment dose of saline was intrathecally administered 15 min before intrathecal administration of R-PIA (0.3, 1.0, or 3.0 μg/10 μl). After measurements of cold and mechanical static allodynia, the animals were sacrificed, and the sciatic nerve was obtained for biochemical estimations.

Groups VI, VII, and VIII: DPCPX- (10 μg/10 μl) and R-PIA-administered (0.3, 1.0, or 3.0 μg/10 μl, intrathecal) vincristine-treated animals (n = 6 /each group)

All procedures were performed in the same serial order as the Groups III, IV, and V. However, a pretreatment dose of DPCPX (10 μg/10 μl) was intrathecally administered instead of saline.

**Statistical analysis**

Data are expressed as mean ± standard error of mean. Data from the behavioral tests were analyzed using the one-way analysis of variance (ANOVA) followed by Tukey's post hoc test, using SigmaPlot® Version 11 software (Systat Software Inc., USA). A P value < 0.05 was considered to be statistically significant.

Results

**Effect of vincristine on hyperalgesia and allodynia**

Compared with the normal group, administration of vincristine resulted in a significant increase in acetone- and pin prick-evoked paw withdrawal duration, indicating the development of cold allodynia (Fig. 2A) and mechanical hyperalgesia (Fig. 2B), respectively. Moreover, the withdrawal latency in the hot plate test was significantly decreased, indicating the development of thermal hyperalgesia (Fig. 2C). The allodynia score in the paint brush test was significantly increased, signifying the development of mechanical dynamic allodynia (Fig. 2D). In addition, the paw withdrawal threshold in response to von Frey filaments was significantly decreased, indicating the development of mechanical static allodynia (Fig. 2E).

**Effect of intrathecal R-PIA administration on cold and mechanical static allodynia in vincristine-treated rats**

Administration of vincristine resulted in a significant increase in acetone-evoked paw withdrawal duration (13.2 ± 0.4 s) compared with the normal group (0.5 ± 0.1 s) on the 28th day. Treatment with intrathecal R-PIA (1.0 and 3.0 μg/10 μl) resulted in a dose-dependent antiallodynic effect against cold allodynia. The antiallodynic effect was higher at the 3.0 μg/10 μl dose of R-PIA (0.7 ± 0.3 s) than at the 1.0 μg/10 μl dose (4.2 ± 0.7 s) (Table 1). Treatment with 0.3 μg/10 μl intrathecal R-PIA, however, did not result in an antiallodynic effect. This attenuating effect peaked 15 min after intrathecal administration of R-PIA (Table 1). After this time, the antiallodynic effect gradually decreased until 180 min. Pretreatment with DPCPX 15 min before intrathecal R-PIA administration significantly reversed the antiallodynic effect of R-PIA (11.4 ± 0.4 g and 11.1 ± 0.3 g for 1.0 and 3.0 μg/10 μl R-PIA, respectively). The data showing the effect of R-PIA administration on cold allodynia are presented in Table 1.

Administration of vincristine resulted in a significant decrease in the paw withdrawal threshold in response to von Frey filaments (1.8 ± 0.3 g), compared with the normal group (15.0 ± 0.0 g). Treatment with intrathecal R-PIA resulted in a dose-dependent antiallodynic effect against mechanical static allodynia. This antiallodynic effect was higher at the 3.0 μg/10 μl dose of R-PIA (14.5 ± 0.3 g) compared with the 1.0 μg/10 μl dose (10.8 ± 0.8 g) (Table 2). Treatment with 0.3 μg/10 μl intrathecal R-PIA did not result in an antiallodynic effect. This attenuating effect peaked 15 min after intrathecal administration of R-PIA (Table 2). After this time, the antiallodynic effect gradually decreased until 180 min.

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Fig. 2. Behavioral examinations following vincristine administration. (A) Cold allodynia assessed by the acetone drop test, (B) Mechanical hyperalgesia assessed by the pin-prick test, (C) Thermal hyperalgesia assessed by the hot plate test, (D) Mechanical dynamic allodynia assessed by the paint brush test, (E) Mechanical static allodynia assessed by the von Frey filament test. Values are presented as mean ± standard error of mean, n = 6 rats per group. One-way ANOVA followed by Tukey’s post hoc test. *P < 0.05 vs. behavioral examination on day 0, †P < 0.05 vs. behavioral examination on day 14.

Table 1. Antiallodynic Effect of Intrathecally Administered R-PIA against Cold Allodynia

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.5 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>V + S + S</td>
<td>13.2 ± 0.4*</td>
<td>13.4 ± 0.4*</td>
<td>12.9 ± 0.4*</td>
<td>12.9 ± 0.3*</td>
<td>13.4 ± 0.4*</td>
<td>12.9 ± 0.4*</td>
<td>13.2 ± 0.4*</td>
<td>13.0 ± 0.4*</td>
</tr>
<tr>
<td>V + S + R-PIA 0.3</td>
<td>12.6 ± 0.3*</td>
<td>11.7 ± 0.6*</td>
<td>11.5 ± 0.4*</td>
<td>11.8 ± 0.5*</td>
<td>12.5 ± 0.3*</td>
<td>11.6 ± 0.4*</td>
<td>12.2 ± 0.4*</td>
<td>12.7 ± 0.3*</td>
</tr>
<tr>
<td>V + DPCPX + R-PIA 0.3</td>
<td>12.7 ± 0.4*</td>
<td>12.6 ± 0.6*</td>
<td>12.3 ± 0.5*</td>
<td>12.1 ± 0.5*</td>
<td>11.8 ± 0.4*</td>
<td>12.4 ± 0.4*</td>
<td>12.2 ± 0.4*</td>
<td>12.7 ± 0.3*</td>
</tr>
<tr>
<td>V + S + R-PIA 1.0</td>
<td>13.2 ± 0.4*</td>
<td>4.2 ± 0.7**</td>
<td>4.9 ± 0.9**</td>
<td>6.8 ± 0.7**</td>
<td>6.6 ± 0.4**</td>
<td>7.7 ± 0.6**</td>
<td>10.0 ± 0.3**</td>
<td>11.0 ± 0.3**</td>
</tr>
<tr>
<td>V + DPCPX + R-PIA 1.0</td>
<td>13.1 ± 0.3*</td>
<td>11.4 ± 0.4**</td>
<td>11.7 ± 0.4**</td>
<td>12.2 ± 0.6**</td>
<td>12.9 ± 0.2**</td>
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<td>V + S + R-PIA 3.0</td>
<td>13.4 ± 0.4*</td>
<td>0.7 ± 0.3**</td>
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</tr>
<tr>
<td>V + DPCPX + R-PIA 3.0</td>
<td>13.0 ± 0.4*</td>
<td>11.1 ± 0.3**</td>
<td>10.6 ± 0.3**</td>
<td>11.2 ± 0.5**</td>
<td>11.2 ± 0.4**</td>
<td>11.7 ± 0.3**</td>
<td>12.7 ± 0.4**</td>
<td>12.9 ± 0.3**</td>
</tr>
</tbody>
</table>

Peripheral neuropathy was induced by the administration of vincristine (100 μg/kg, i.p.) for 10 days. On the 28th day, saline or DPCPX (10 μg/10 μl) was intrathecally administered 15 min before intrathecal R-PIA administration (1.0 μg/10 μl or 3.0 μg/10 μl). Cold allodynia was then assessed using the acetone drop test (seconds). Results are expressed as mean ± standard error of mean, n = 6 rats per group. One-way ANOVA followed by Tukey’s post hoc test. *P < 0.05 vs. normal control group, †P < 0.05 vs. vincristine control group, ‡P < 0.05 vs. R-PIA 1.0 μg/10 μl group, §P < 0.05 vs. R-PIA 3.0 μg/10 μl group. V: vincristine, S: saline, DPCPX: 1,3-dipropyl-8-cyclopentylxanthine = adenosine A₁ receptor antagonist, R-PIA: N6-(2-phenylisopropyl)-adenosine R-(-)isomer = adenosine A₁ receptor agonist.

https://doi.org/10.4097/kja.19481
Peripheral neuropathy was induced by the administration of vincristine (100 μg/kg, i.p.) for 10 days. On the 28th day, saline or DPCPX (10 μg/10 μl) was intrathecally administered 15 min before intrathecal R-PIA administration (1.0 μg/10 μl or 3.0 μg/10 μl). Mechanical static allodynia was then assessed using the von Frey filament test (gram). Results are expressed as mean ± standard error of mean, n = 6 rats per group. One-way ANOVA followed by Tukey’s post hoc test. *P < 0.05 vs. normal control group, †P < 0.05 vs. vincristine control group, ‡P < 0.05 vs. R-PIA 1.0 μg/10 μl group, §P < 0.05 vs. R-PIA 3.0 μg/10 μl group. V: vincristine, S: saline, DPCPX: 1,3-dipropyl-8-cyclopentylxanthine = adenosine A1 receptor antagonist, R-PIA: N6-(2-phenylisopropyl)-adenosine R-(-)-isomer = adenosine A1 receptor agonist.

### Table 2. Antiallodynic Effect of Intrathecally Administered R-PIA against Mechanical Static Allodynia

<table>
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<th>Time (min)</th>
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<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
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<td>14.9 ± 0.1</td>
<td>15.0 ± 0.0</td>
<td>14.9 ± 0.1</td>
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<td>14.9 ± 0.1</td>
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</tr>
<tr>
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<td>1.6 ± 0.4*</td>
<td>2.2 ± 0.3*</td>
<td>2.1 ± 0.4*</td>
<td>2.1 ± 0.4*</td>
<td>1.8 ± 0.4*</td>
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<tr>
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<td>3.6 ± 0.3*</td>
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<td>V + DPCPX + R-PIA 0.3</td>
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<tr>
<td>V + S + R-PIA 1.0</td>
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<td>V + DPCPX + R-PIA 1.0</td>
<td>1.9 ± 0.2*</td>
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<tr>
<td>V + S + R-PIA 3.0</td>
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<tr>
<td>V + DPCPX + R-PIA 3.0</td>
<td>2.0 ± 0.2*</td>
<td>3.9 ± 0.3*</td>
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<td>2.1 ± 0.2*</td>
</tr>
</tbody>
</table>

Pretreatment with DPCPX (10 μg/10 μl) 15 min before intrathecal R-PIA administration significantly reversed the antiallodynic effect of R-PIA (3.6 ± 0.4 g and 3.9 ± 0.3 g for R-PIA 1.0 and 3.0 μg/10 μl, respectively). The data showing the effect of R-PIA administration on mechanical static allodynia are presented in Table 2.

### Effect of intrathecal R-PIA on TNF-α level and MPO activity in vincristine-treated rats

Administration of vincristine resulted in a significant increase in TNF-α level in tissue from the sciatic nerve (12.3 ± 0.6 pg/mg) compared with the normal group (4.1 ± 0.3 pg/mg). Intrathecal administration of R-PIA significantly reversed this increase in TNF-α level in a dose-dependent manner (9.0 ± 0.3 and 6.4 ± 0.4 pg/mg for R-PIA 1.0 and 3.0 μg/10 μl, respectively). Intrathecal administration of 0.3 μg/10 μl R-PIA did not affect the TNF-α level (Fig. 3A). Pretreatment with DPCPX before treatment with intrathecal R-PIA significantly reversed this attenuating effect of R-PIA (10.7 ± 0.4 and 10.7 ± 0.4 pg/mg for R-PIA 1.0 and 3.0 μg/10 μl, respectively) (Fig. 3A).

Administration of vincristine also resulted in a significant increase in MPO activity in tissue from the sciatic nerve (0.9 ± 0.1 U/mg) compared with the normal group (0.2 ± 0.0 U/mg). Intrathecal administration of R-PIA significantly reversed this increase in MPO activity in a dose-dependent manner (0.5 ± 0.0 and 0.3 ± 0.1 U/mg for R-PIA 1.0 and 3.0 μg/10 μl, respectively) (Fig. 3A). Intrathecal administration of 0.3 μg/10 μl R-PIA did not affect MPO activity (Fig. 3B). Pretreatment with DPCPX before treatment with intrathecal R-PIA significantly reversed this attenuating effect of R-PIA (0.8 ± 0.0 and 0.7 ± 0.1 U/mg for R-PIA 1.0 and 3.0 μg/10 μl, respectively) (Fig. 3B).

### Discussion

Vincristine is a well-known chemotherapeutic agent widely used for the treatment of several malignancies such as breast cancer, leukemia, lymphoma, and primary brain tumors [18]. Nevertheless, sometimes neurotoxicity of the peripheral nerve fibers or sensory-motor neuropathy can develop during vincristine treatment. In the present study, intraperitoneal administration of vincristine (100 μg/kg) for 10 days caused the development of cold allodynia, mechanical dynamic and static allodynia, and mechanical and heat hyperalgesia, evaluated on the 14th and 28th day of the experiment. Mechanical dynamic allodynia is induced by light touching of the skin with a soft brush. Meanwhile, mechanical static allodynia is elicited by static pressure stimulation applied to the skin. Clinically, mechanical dynamic allodynia is a more common symptom than mechanical static allodynia. Therefore, the measurement of mechanical dynamic allodynia is preferred over mechanical static allodynia. It has been known that mechanical dynamic allodynia is mediated by peripheral low threshold, large myelinated Aβ-fibers [19]. The behavioral alterations observed in our study are consistent with those in previous studies demonstrating the development of pain symptoms following chronic vincristine administration [20]. Vincristine administration (0.1 mg/d) for 10 days (two 5-day cycles with a 2-day pause in between) was shown to produce persistent mechanical hyperalgesia and allodynia 5–8 days after peritoneal administration of vincristine, with this effect peaking after two weeks [10].

In the present investigation, treatment with intrathecal R-PIA after the development of vincristine-induced neuropathy significantly reversed behavioral changes, including paw cold allodynia and mechanical static allodynia. The antiallodynic effect of intra-
The effect of different pharmacological interventions on inflammatory and neuropathic models exhibiting hyper-re sponseness. Additionally, the potential of adenosine A_1 receptor agonists as therapeutic agents for pain has been considered in previous reports [6,21]. Subsequent preclinical studies have further illustrated the antinociceptive and/or anti-hyperalgesic actions of adenosine A_1 receptor agonists in a diverse range of pain models. These models include the formalin model of inflammation, the carrageenan model of arthritis, hyperalgesia following surgical incision, the chronic constriction injury model of neuropathic pain, the spinal nerve ligation model of neuropathic pain, pain following spinal cord injury, and the streptozotocin model of diabetic neuropathy. This is an ongoing field of research, and reviews on the analgesic action of adenosine A_1 receptor agents have been recently published [22].

Adenosine A_1 receptors are located on peripheral sensory nerve endings [23], within the superficial layers of the dorsal horn of the spinal cord [24] and at specific supraspinal sites within the pain signaling neuraxis [25]. In addition to their neuronal localization, adenosine A_1 receptors have also been identified on microglia [26], and their inhibition has been shown to contribute to antinociception in instances where the pain state involves glial activation and hypertrophy [26]. Adenosine A_1 receptor signaling at the cellular level acts via the activation of an associated G protein; inhibition of cyclic AMP/ PKA and interactions with Ca^{2+} and K^+ channels are mediated via the Gαi subunit, and interactions with the PLC/IP₃/DAG pathway via the Ga or βγ subunits. Additionally, adenosine A_1 receptor signaling can involve β-arrestin-mediating receptor uncoupling and downregulation [27]. Several alternative clinical applications for adenosine A_1 receptor agents in cardiovascular, respiratory, neuroprotective, and metabolic conditions are currently being explored [28].

Several studies have reported that intrathecal administration of adenosine A_1 receptor agonists produces pain-reducing effects in animal models such as the spinal nerve ligation model of neuropathic pain and the formalin model of inflammation [18,29]. In the present study, intrathecally administered R-PIA at a dose of 1.0–3.0 μg/10 μl also produced an antiallodynic effect in a rat model of VIPN. Considering the dose of intraperitoneal R-PIA was 20–25 μg/kg (= 4.0–6.25 μg) [30,31] in previous studies, the intrathecal dose of R-PIA was only 25–48% of the intraperitoneal dose of R-PIA. A smaller dose is utilized when R-PIA is administered intrathecally; therefore, side effects are reduced. This is the first report suggesting the neuropathy-attenuating potential of intrathecal R-PIA in the VIPN model of rats.

In the present investigation, the anti-inflammatory effect of intrathecally administered R-PIA was also investigated. There exist a limited number of studies that have investigated the anti-inflammatory effects of R-PIA [32–34]. In one such study, inflammatory
pain was induced in rats by an injection of Complete Freund’s Adjuvant (20 μl) into the plantar surfaces of hind paws. Electrophysiological recordings then suggested that the adenosine A3 receptor may potentiate glycinegic transmission through Gα5/PKA/α3 and Gβγ/α1′′′ pathways [32]. Furthermore, another study concluded that the cochlea expresses adenosine A3 receptors, which mediate tonic suppression of oxidative, inflammatory, and apoptotic processes. The protective role of adenosine against cisplatin ototoxicity was shown to be enhanced by inhibition of the NOX3/STAT1 signaling pathway [33]. Adenosine, lidocaine, and Mg2+ fluid therapy attenuated systemic inflammation, platelet dysfunction, and coagulopathy after non-compressible truncal hemorrhage in another study [34].

In the present study, we measured TNF-α levels in tissue surrounding the sciatic nerve as a biochemical surrogate marker of vincristine-induced inflammation. We found that vincristine treatment increased the level of TNF-α in this tissue. Inflammatory stimuli release reactive species such as NO• and •O−, proinflammatory factors such as TNF-α, and pronociceptive mediators such as cytokines [35]. TNF-α is a major proinflammatory cytokine, and increased TNF-α levels are associated with pathological pain [36]. This vincristine-induced elevation in TNF-α level was markedly reduced with intrathecal administration of R-PIA (1.0 and 3.0 μg/10 μl). These data suggest that intrathecal R-PIA has anti-inflammatory effects. In the present study, the MPO enzyme level in tissue around the sciatic nerve was increased after administration of vincristine for a period of 10 days. MPO is released from neutrophils and is a significant marker of inflammation. Among the various mechanisms involved in vincristine-induced neuropathy, inflammatory reaction has been described to play a significant role in the pathophysiology of nerve toxicity [37]. Long-term administration of vincristine activates spinal glial cells and up-regulates cytokines in these cells, leading to hyperalgesia and allodynia [38]. Vincristine damages Schwann cells, which causes demyelination [39], and damaged Schwann cells then mediate the release of inflammatory cytokines and chemokines including monocyte chemo-attractant protein-1 [39]. These series of processes are responsible for the infiltration of leucocytes, lymphocytes, and macrophages to the site of nerve injury, further augmenting the inflammatory environment and producing nerve damage [38]. In our study, the vincristine-induced increase in MPO activity was significantly reduced following intrathecal administration of R-PIA (1.0 and 3.0 μg/10 μl). The MPO data also suggested that intrathecal R-PIA has anti-inflammatory effects. Based on both the TNF-α and MPO data, the intrathecal R-PIA-mediated decrease in allodynia (both cold and mechanical static) observed in the VIPN model may be a result of its anti-inflammatory properties. This is the first report demonstrating the anti-inflammatory effect of intrathecal R-PIA in vincristine-induced neuropathic pain in rats. Therefore, given the existing literature and the data obtained from this study, it seems that intrathecally administered R-PIA exerts beneficial effects in a rat model of VIPN by virtue of its anti-inflammatory actions, specifically the inhibition of TNF-α levels and MPO activity. In the present study, there are some limitations such as the relationship between the antiallodynic and anti-inflammatory effect of intrathecal R-PIA that needs to be more fully defined. Further investigations are required to evaluate the close relationship between them.

In conclusion, the results of the present study suggest that intrathecally administered R-PIA attenuates neuropathic cold and mechanical static allodynia in the VIPN model of rats, partially due to its anti-inflammatory actions. Further studies are required to evaluate the involvement of the anti-inflammatory effects of R-PIA in VIPN.

Conflicts of Interest

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

Author Contributions

Kyungmi Kim (Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Writing – original draft)
Wonyeong Jeong (Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Writing – original draft)
In Gu Jun (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization)
Jong Yeon Park (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation)

ORCID

Kyungmi Kim, https://orcid.org/0000-0003-2833-1912
Wonyeong Jeong, https://orcid.org/0000-0002-7025-7210
In Gu Jun, https://orcid.org/0000-0002-1225-1793
Jong Yeon Park, https://orcid.org/0000-0003-0588-1903

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The erector spinae plane (ESP) block is a novel interfascial regional analgesic technique that was described by Forero et al. [1] in 2016, to treat thoracic neuropathic pain. Growing evidence of its efficacy and relative simplicity of performance has resulted in an increase in its use for managing acute and chronic pain [2–5]. The spread of local anesthetic through the paravertebral spaces is thought to be responsible for its analgesic effect on somatic and visceral pain, and thus, it has been reported to be as effective as thoracic epidural analgesia when administered bilaterally [6].

The ESP block may have some advantages over thoracic epidural analgesia, as it is a moderately simple technique that can be used unilaterally. It provides lesser sympathetic blockade with fewer cardiovascular effects, compared to the paravertebral block. However, the administration of the ESP block requires ultrasonographic guidance.

The ESP block seems to be similar to a superficial block compared to the epidural and paravertebral blocks, with a lower risk of hemorrhage, especially in patients with altered hemostasis, i.e., the risk of spinal hematoma and spinal cord compression is lower, as the block is administered superficial to the transverse processes, allowing the spinal cord to be protected by the vertebral canal. However, these aspects have not been studied in depth and established firmly in current literature [7].

We describe a case series of 5 patients with altered hemostasis (activated partial thromboplastin time [aPTT] ratio or international normalized ratio [INR] exceeding 1.5 times the normal value, a platelet count equal to or below 80000/μl, or use of anticoagulant...
medication) in whom the ESP block was performed for acute pain management. The risks of the technique were described to all the patients and discussed with them or their legal representatives. We believed that the benefits outweighed the risks of the technique in each patient. All procedures were performed by one of the two principal authors. We monitored the patients daily for the first 5 days after the technique. No neurologic or hemorrhagic complications were recorded.

There seems to be growing evidence supporting the fact that the ESP block is a superficial block. We believe that the relationship with the surrounding anatomical structures, absence of major vessels in the vicinity, compressibility, and the use ultrasonographic guidance are facts that support this argument.

Case Reports

We described a series of 5 patients in whom inadequate acute pain control caused difficulty in weaning them off the ventilator. Conventional neuraxis analgesia techniques, namely epidural or paravertebral blocks, were contraindicated due to a well-established risk of severe bleeding and spinal cord compression. All the potential risks and benefits were discussed with all patients when possible, or their legal guardians, and verbal and written informed consent were obtained in all situations for reporting these cases. All procedures were performed under ultrasonographic guidance (M-Turbo®, Sonosite Inc., USA), using a linear high-frequency probe (HFL38x®, Sonosite Inc., USA) in the longitudinal position, after identifying the transverse processes of the desired vertebra. Once identified, a 100-mm needle (Echoplex®, Vygon, France) was inserted in plane along the cephalad to caudal direction, until the needle tip contacted bone, between the erector spinae muscle and the transverse process.

Daily assessment of potential complications was performed for 5 days.

We have described all the clinical cases and the rationale behind our decision-making process as follows.

Case 1

A male patient, weighing 88 kg, was diagnosed with septic shock caused by acute necrotizing pancreatitis with multiorgan disfunction and altered hemostasis (thrombocytopenia: 18000/μl, INR: 2.52, and aPTT: 45.2/29 s). Poor acute pain management with a multimodal strategy with paracetamol (4 g/day), ketamine (0.3 mg/kg/h), gabapentin (1400 mg/day), and morphine (300 mg/day) caused difficulty in ventilator weaning. We performed a continuous left ESP block at the level of T10 using 0.375% ropivacaine (20 ml every 6 h), which produced a better analgesic effect over 5 days (maximum NPS score of 3/10) and reduced the daily dose of morphine to 44 mg/day. No technique-related complications were observed.

Case 2

A 16-year-old boy, weighing 80 kg, was admitted to the pediatric intensive care unit due to polytraumatism. He had pelvic fracture, right femoral fracture, and severe lesions of the right femoral artery and vein, which were responsible for below-knee amputation of the lower right limb. A multimodal strategy with paracetamol (3 g/day), metamizol (4 g/day), ketamine (0.3 mg/kg/h), gabapentin (1400 mg/day), and morphine (300 mg/day) afforded poor pain control in the lower limb, which was consistent with neuropathic pain (Douleur Neuropathique 4 [DN4] score of 6/10, NPS score of 6/10 at rest, and 10/10 during nursing care, needed twice daily). He also presented with persistent altered hemostasis (INR: 1.8–2.24).

We performed a continuous ESP block at the level of T10 using 0.375% ropivacaine (20 ml every 6 h), which produced a better analgesic effect over 5 days (maximum NPS score of 3/10) and reduced the daily dose of morphine to 44 mg/day. No technique-related complications were observed.

Case 3

A 69-year-old man was admitted to the intensive care unit due to hemorrhagic shock after elective open splenectomy and left nephrectomy, due to refractory immune thrombocytopenic purpura and left kidney tumour. He had a left subcostal incision, approximately 30 cm in length. His usual platelet count was around 30000–40000/μl, which plummeted to a minimum count of 5000/μl.

Poor acute pain management with a multimodal strategy with paracetamol (4 g/day), ketamine (0.5 mg/kg/h), and morphine (140 mg/day) caused difficulty in ventilator weaning. We performed a continuous left ESP block at the level of T7 with 0.2% ropivacaine (20 ml every 4 h), which allowed adequate
analgesia and extubation after 6 h.

No technique-related complications were observed.

**Case 4**

A 71-year-old man was admitted to the intensive care unit after open endoluminal aortic thrombectomy, with a left subcostal incision, and a thoracotomy at the level of the sixth intercostal space.

Post-operative systemic anticoagulation was required after surgery and he was also under anticoagulant therapy with enoxaparin (1 mg/kg/day, adjusted for acute kidney injury and an estimated glomerular filtration rate below 30 ml/min) and presented with thrombocytopenia (platelet count: 80000/μl).

He experienced acute pain with an NPS score of 7/10 despite a multimodal analgesic regimen with paracetamol (4 g/day), ketamine (0.2 mg/kg/h), and fentanyl (3 μg/kg/h), which did not permit ventilatory weaning.

We performed a continuous left ESP block at the level of T6, with 0.2% ropivacaine (20 ml every 4 h), which produced adequate analgesia, permitting extubation after 4 h.

No technique-related complications were observed.

**Case 5**

A 21-year-old man was admitted to the intensive care unit due to hemorrhagic shock caused by a massive left hemothorax and hypertensive pneumothorax after penetrating thoracic trauma, which was complicated by cardiac arrest. Emergency atypical lung resection was performed with a left thoracotomy at the level of the sixth intercostal space.

Thrombocytopenia was observed (43000/μl) despite correction of INR and aPTT.

A multimodal regimen with paracetamol (4 g/day), ketamine (0.3 mg/kg/h) and fentanyl (3 μg/kg/h) provided poor pain control as an NPS score of 9/10 was recorded, which made ventilator weaning difficult.

We performed a continuous left ESP block at the level of T5, with 0.2% ropivacaine (20 ml every 4 h), and adequate analgesia was achieved, which allowed extubation after 4 h.

No technique-related complications were observed.

**Discussion**

Few regional analgesia techniques are available for ameliorating thoracic or abdominal visceral pain (such as the thoracic or lumbar epidural or paravertebral block) for patients with altered hemostasis. The ESP block is a fascial plane block, which is performed between the transverse processes and erector spinae muscles, with a moderate level of difficulty, and can provide adequate analgesia through multiple dermatomes by cephalocaudal spread, as reported by Ivanusic et al. [8]. Although this study reported no spread of dye to the ventral rami, several (published) studies have provided evidence, supporting the idea that anterior spread of local anesthetic provides visceral fiber blockade, explaining its use in thoracic, cardiac and abdominal surgery [9–13]. A recent case report described Harlequin syndrome after the ESP block, which is clearly consistent with the anterior spread of local anesthetic solution responsible for sympathetic fiber chain blockade [14].

We believe that although the anterior spread of the dye has not been well-established in cadaveric studies, a sufficient number of clinical reports currently support the existence of anterior spread that is responsible for the visceral analgesia provided by this block. We believe that the lack of dye spread in cadavers may be dependent on the lack of thoracic wall movement caused by respiratory movement (either spontaneous breathing or by mechanical ventilation), which may be a major factor that facilitates anterior spread of the local anesthetic.

We achieved adequate analgesia in all patients. We observed 70% to 89% of reduction in the NPS scores and 83% to 100% reduction in opioid consumption (Table 1). This amelioration in pain allowed all patients to be successfully weaned off the ventilator, within the next few hours.

There is a safe distance between the anatomical fascial plane and neuraxis or pleura, which renders this block suitable for patients with altered hemostasis under ultrasonographic guidance. This hypothesis has not been tested in randomized controlled trials and the safety of this technique in these circumstances has not been tested yet.

We used this technique in 5 patients with major alterations in hemostasis, such as severe thrombocytopenia, INR > 1.5, and one patient under therapeutic anticoagulation with low molecular weight heparin.

We did not observe any neurological complications, including spinal hematoma or nerve root compression, or hemorrhagic complications, including internal or external bleeding 5 days after administration of the ESP block.

Although these observations may represent a small pool of patients, it is the largest sample of such patients to the best of our knowledge and may represent a major contribution that establishes the safety of this block in patients with altered hemostasis.

The duration of mechanical ventilation and use of deep sedation have been linked with increased mortality and delirium in intensive care practice. An adequate analgesic regimen allows pa-
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Diagnosis / Procedure</th>
<th>Maximum NPS (0–10)</th>
<th>Initial analgesic regimen</th>
<th>Opioid in equivalent morphine daily dose</th>
<th>Altered hemostasis</th>
<th>Level of ESP block</th>
<th>Single-shot vs continuous technique</th>
<th>Local anesthetic regimen</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute necrohemo-orragic pancreatitis with multiorganic dysfunction</td>
<td>N/A</td>
<td>Paracetamol (3 g/day) Ketamine (0.15 mg/kg/h) Fentanyl (2.5 μg/kg/h)</td>
<td>245 mg 24 mg</td>
<td>Yes (2.52) Yes (1.55X) Yes (18,000/μl)</td>
<td>T7</td>
<td>Single-shot</td>
<td>0.5% ropivacaíne 20 ml, bilaterally</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Right lower limb amputation (below knee)</td>
<td>10</td>
<td>Paracetamol (3 g/day) Metamizol (4 g/day) Ketamine (0.3 mg/kg/h) Gabapentin (1400 mg/day) Morphine (300 mg/day)</td>
<td>300 mg 44 mg</td>
<td>Yes (1.8 - 2.24) No No (85,000/μl)</td>
<td>T10</td>
<td>Continuous</td>
<td>0.375% ropivacaíne 20 ml every 6 h</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Open splenectomy and left nephrectomy</td>
<td>10</td>
<td>Paracetamol (4 g/day) Ketamine (0.5 mg/kg/h) Morphine (140 mg/day)</td>
<td>140 mg 0 mg</td>
<td>No No Yes (5,000/μl)</td>
<td>T7</td>
<td>Continuous</td>
<td>0.2% ropivacaíne 20 ml every 4 h</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Open endoluminal aortic thrombectomy</td>
<td>7</td>
<td>Paracetamol (4 g/day) Ketamine (0.2 mg/kg/h) Fentanyl (3 μg/kg/h)</td>
<td>288 mg 0 mg</td>
<td>Therapeutic anticoagulation Yes (80,000/μl)</td>
<td>T6</td>
<td>Continuous</td>
<td>0.2% ropivacaíne 20 ml every 4 h</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Left thoracotomy</td>
<td>9</td>
<td>Paracetamol (4 g/day) Ketamine (0.3 mg/kg/h) Fentanyl (3 μg/kg/h)</td>
<td>252 mg 0 mg</td>
<td>No No Yes (43,000/μl)</td>
<td>T5</td>
<td>Continuous</td>
<td>0.2% ropivacaíne 20 ml every 4 h</td>
<td>No</td>
</tr>
</tbody>
</table>

Values are presented as number (%). ESP: erector spinae plane, INR: international normalized ratio, aPTT: activated partial thromboplastin time, 1.5X: 1.5 times the normal value, N/A: not applicable.
patients to be mechanically ventilated with a lower level of sedation for the shortest time possible, which allows for quicker ventilatory weaning and extubation, which are the primary goals in this setting. The ESP block is a regional analgesic technique with a moderate level of difficulty, which can be used in patients with altered hemostasis and inadequate pain control and which allows them to be quickly and successfully weaned from the ventilator. This may be particularly important in patients who have experienced trauma and those who have undergone surgery, since this technique may decrease the duration of mechanical ventilation and eventually reduce mortality. We think that these aspects are particularly interesting and deserve further study [15].

Nevertheless, we strongly believe that an individualized risk-benefit assessment should be performed for every patient and that more studies are needed to support our hypothesis.

Conflicts of Interest

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

Author Contributions

João Galacho (Conceptualization; Data curation; Formal analysis; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing)
Mariano Veiga (Conceptualization; Data curation; Formal analysis; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)
Lucindo Ormonde (Supervision)

ORCID

João Galacho, https://orcid.org/0000-0001-9819-6176
Mariano Veiga, https://orcid.org/0000-0002-8018-1299
Lucindo Ormonde, https://orcid.org/0000-0002-9981-6573

References

The ultrasound-guided infraclavicular block (ICB) has several potential advantages for a single shot and continuous block of the brachial plexus [1,2]. Currently, the techniques for ICB include the lateral parasagittal, costoclavicular, and retroclavicular in-plane approaches [3–5]. Out of these, the lateral parasagittal approach in which the needle tip is placed posterior to the artery is most widely practiced. The injection of local anesthetics (LAs) posterior to the axillary artery (AA) produces a U-shape hypoechoic shadow, which has been famously described as a double-bubble sign [6]. Compared to the lateral parasagittal approach, the ultrasound-guided costoclavicular approach produces more rapid and effective anesthesia as the brachial plexus cords are closely clustered in the costoclavicular space [7,8].

Studies using the frontal slab technique of magnetic resonance neurography showed the subcoracoid tunnel beneath the pectoralis minor in an oblique longitudinal plane [9–11]. Based on that finding, we propose a novel approach to ICB, which we describe as the “subcoracoid tunnel block.” In this approach, with the ultrasound scan along the brachial line, the cords of brachial plexus are visualized in the infraclavicular area below the pec-
toralis minor muscle [12]. In this case series, we employed the subcoracoid tunnel block for 20 patients undergoing below-elbow surgery. Our primary aim was to assess the needle-cord visualization on ultrasound when performing the block. Our secondary aim was to evaluate the identification of cords on neurostimulation, block success rate, and complications if any.

**Case Report**

Twenty patients aged 20 to 60 years undergoing below-elbow surgery under the subcoracoid tunnel block were enrolled for this case series from January 2019 to December 2019 after obtaining approval of the hospital’s ethical committee (Sancheti Institute of Orthopedics and Rehabilitation, Pune, India). Written informed consent was obtained from all patients. Patients with an American Society of Anesthesiologist physical status greater than III, pregnancy, neuromuscular diseases, skin infections at the needle insertion site, a prior surgery in the infraclavicular fossa, a history of brachial plexus injuries, a bleeding disorder or an allergy to LAs were excluded.

In the supine position, the patient’s infraclavicular area was cleaned with an antiseptic solution and draped with sterile sheets; the linear ultrasound probe was wrapped in sterile Tegaderm. Sedation was not induced before or during the block procedure. For the subcoracoid tunnel block, the ultrasound probe was placed along the brachial line formed by joining the external surface landmarks C6 tubercle, mid-clavicular point, and AA [11]. The probe was placed with its proximal end towards the mid-clavicular point and distal end with a marker towards the apex of the axilla (Fig. 1A). The ultrasound scan demonstrated the AA sandwiched between the cords of the brachial plexus in the subcoracoid tunnel. The probe position and needle entry point at the probe’s distal end were marked for the in-plane needle approach from a caudal to cephalad direction (Fig. 1B). With a slight lateral or medial tilt of the probe, the cords were seen around the AA.

A 100-mm nerve stimulator needle connected to the nerve stimulator was used for the block. A medial tilt demonstrated the posterior (posterior and medial to the AA) and medial (anterior and medial cord to the AA) cords, while a slight lateral tilt of the probe demonstrated the lateral cord (anterior and lateral to the AA). Neurostimulation at 0.4 Ma was applied to identify these cords during the first pass. The probe was tilted medially, and the needle was advanced to position its tip above the posterior or medial cord. After neurostimulation and desired muscle contractions (posterior cord: extension of metacarpophalangeal joints; medial cord: flexion of the metacarpophalangeal joints), the LA was injected (Fig. 2A). The probe was tilted laterally. The needle tip was repositioned above the lateral cord, and the LA was injected (Fig. 2B). A total of 30 ml of 0.5% bupivacaine (25 ml at the posterior or medial cord and 5 ml at the lateral cord) with 1 μg/kg clonidine was injected in 5-ml boluses.

During the block, ultrasound images at the following points were saved: (1) the scan along the brachial line in the oblique longitudinal plane; (2) medial tilt and needle contact with the cord and LA injection; and (3) lateral tilt and needle contact with the cord and LA injection. All images were downloaded on a hard drive.

![Fig. 1. Probe placement and needle insertion along the brachial line. (A) The linear probe is placed parallel to the brachial line that joins the AA, mid-point of the clavicle, and C6 tubercle. (B) The needle is inserted in-plane and in a caudal to cephalad direction along the brachial line. The probe is then tilted medially or laterally to visualize the medial/posterior cords or lateral cord, respectively. The marker of the probe is caudal towards the axilla. AA: axillary artery, OLA: oblique longitudinal axis, SCM-MH: medial head of the sternocleidomastoid muscle, SCM-LH: lateral head of the sternocleidomastoid muscle, C6: Chassaignac's tubercle.](https://doi.org/10.4097/kja.20372)
For each block, the visibility of contact of the needle tip with the cords on ultrasound images was scored on a 5-point scale; 1: 0–20%, 2: 20–40%, 3: 40–60%, 4: 60–80%, 5: 80–100%.

Patients were assessed at 5-min intervals after the LA injection for the onset of sensory and motor blocks. The sensory block was assessed by loss of pain to a pinprick in the dermatomal areas of the forearm (lateral, medial, and posterior aspects) and the arm (medial and posterior). The motor block was assessed by loss of elbow flexion (musculocutaneous nerve), wrist flexion (median nerve), wrist extension (radial nerve), and flexion of the last two little fingers (ulnar nerve). The onset times for sensory and motor blocks were recorded. The subcoracoid tunnel block was considered successful if there was complete sensory anesthesia of the forearm, no incisional pain, and no need for additional supplementation with intravenous fentanyl, midazolam, or propofol during the surgery. Postoperatively, patients were assessed for the first analgesic request time (visual analogue scale score > 3) and complete motor block recovery. The subcoracoid tunnel block was successful in 16/20 (80%) patients. One patient had pain at the incision site, and 3 patients complained of mild to moderate pain on the manipulation of fracture fragments. In the patient with incision site pain, the block was supplemented with infiltration of 1% lignocaine (10 ml) along the incision line. The other 3 patients were administered with intermittent boluses of fentanyl 1 μg/kg and midazolam 0.03 mg/kg iv for completion of the surgery. At the follow-up at discharge, no significant complications were seen in any patient.

Discussion

In our case series, the visibility of contact of the needle tip with the cords in the subcoracoid tunnel block was 5 in all 20 patients (80–100% visibility). On neurostimulation, the posterior cord was identified in 11 (55%) patients and medial cord in 9 (45%) patients. The subcoracoid tunnel block provided effective surgical anesthesia in 16 (80%) patients. The block could be performed in all patients without technical difficulties or complications.

To our knowledge, the subcoracoid tunnel block has not been previously described in the literature. This technique offers several advantages, including good visibility of the neural structures.
along the length of the brachial plexus. Compared to the traditional lateral parasagittal approach, the needle is better visualized in the subcoracoid tunnel block. During the scan along the brachial line, the AA is seen initially sandwiched between the cords, and a slight medial or lateral tilt leads to the disappearance of the artery bringing the cords in view. This allows safe placement of the needle tip close to the cords. Pneumothorax has been reported in both lateral parasagittal and costoclavicular approaches [13–15]. As the needle in the subcoracoid tunnel block is inserted caudad to cephalad, it is always directed away from the pleura, thus minimizing the chances of pneumothorax. The 2-dimensional spread of LA is also easy to visualize as it is seen hydro-dissecting in a longitudinal axis between the cords of the brachial plexus.

The frontal slab technique of magnetic resonance neurography generates bright images of the brachial plexus in the longitudinal axis [9–11]. Akin to this, we performed ultrasound with a probe below the clavicle along the brachial line. The brachial line (surface landmarks, C6, mid-point of the clavicle, and the AA) coincided with the oblique longitudinal axis of magnetic neurography that identified the brachial plexus in the subcoracoid tunnel [12]. The ultrasound images along the brachial line demonstrated the positions of posterior, medial, and lateral cords as medial and posterior, medial and anterior, and lateral and anterior to the AA, respectively (Figs. 2A and 2B).

The limitation of our study was the small size of the case series. Unlike the traditional lateral parasagittal approach to ICB in which the needle is positioned below the AA, the subcoracoid tunnel block requires a slight medial or lateral tilt of the probe together with the withdrawal and redirection of the needle tip to place it near the cords. Further comparative studies of the subcoracoid tunnel block with traditional lateral parasagittal and costoclavicular approaches are required to evaluate its safety and efficacy.

To conclude, the subcoracoid tunnel block is an easy, safe, and effective alternative approach for ICB. The ultrasound scan along the brachial line below the clavicle aligns the ultrasound beam parallel to the cords of the brachial plexus, generating a longitudinal image of the brachial plexus cords. With the needle inserted in-plane just below the ultrasound probe, the entire needle path and its tip close to the neural targets can be visualized.

Conflicts of Interest

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Author Contributions

Sandeep Diwan (Conceptualization; Investigation; Methodology; Project administration; Writing – original draft)
Divya Sethi (Data curation; Formal analysis; Visualization; Writing – review & editing)
Avinash Gaikwad (Data curation; Investigation; Software; Writing – original draft)
Parag Sancheti (Project administration; Resources; Validation; Visualization)
Abhijit Nair (Data curation; Supervision; Visualization; Writing – review & editing)

ORCID

Sandeep Diwan, https://orcid.org/0000-0001-7950-070X
Divya Sethi, https://orcid.org/0000-0003-2319-2765
Avinash Gaikwad, https://orcid.org/0000-0002-5689-9735
Parag Sancheti, https://orcid.org/0000-0002-8903-1430
Abhijit Nair, https://orcid.org/0000-0003-2506-0301

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Ultrasound-guided percutaneous intercostal nerve cryoneurolysis for analgesia following traumatic rib fracture
-a case series-

John J. Finneran IV1, Rodney A. Gabriel1, Matthew W. Swisher1, Allison E. Berndtson2, Laura N. Godat2, Todd W. Costantini2, Brian M. Ilfeld1

Departments of 1Anesthesiology, 2Surgery, University of California, San Diego, La Jolla, CA, USA

Background: Rib fractures are a common injury in trauma patients and account for significant morbidity and mortality within this population. Local anesthetic-based nerve blocks have been demonstrated to provide significant pain relief and reduce complications. However, the analgesia provided by these blocks is limited to hours for single injection blocks or days for continuous infusions, while the duration of this pain often lasts weeks.

Case: This case series describes five patients with rib fractures whose pain was successfully treated with cryoneurolysis.

Conclusions: Ultrasound-guided percutaneous cryoneurolysis is a modality that has the potential to provide analgesia matching the duration of pain following rib fractures.

Keywords: Analgesia; Cryoablation; Nerve block; Rib fracture; Trauma; Ultrasound.
who underwent ultrasound guided percutaneous intercostal cryoneurolysis for rib fracture pain (three who received only cryoneurolysis therapy and two who received both cryoneurolysis and a local anesthetic block) with sustained analgesia following the procedure.

**Case Reports**

The University’s Institutional Review Board (University of California San Diego) waives review requirements for short case series. Written informed consent for the cryoneurolysis procedure and publication of relevant, non-identifiable history and imaging in the form of a case report was obtained from all patients.

**Case 1**

An 80-year-old female with a history of type-II diabetes mellitus, hypertension, congestive heart failure, and chronic kidney disease presented after falling out of bed with left-sided 4th through 8th rib fractures. Despite aggressive treatment in the intensive care unit, the patient’s pulmonary status deteriorated over the following 24 hours and she was intubated for respiratory failure. During trials of spontaneous breathing the following morning, the patient was unable to take adequate tidal volumes and rapidly desaturated. Single-injection local anesthetic-based intercostal nerve blocks and cryoneurolysis to each intercostal nerve associated with a fractured rib (left 4th – 8th) was planned in the hope that the analgesia from the cryoneurolysis would not only facilitate extubation, but also provide long lasting relief.

The patient was positioned prone in a ProneView cushion (Mizuho OSI Inc., USA) and the 4th–8th ribs were identified using a curvilinear ultrasound transducer (SonoSite M-Turbo®, USA). At each level, an intercostal nerve block was performed just distal to the costotransverse joint, using an in-plane ultrasound guided technique and 20-gauge Tuohy needle to deliver 4 ml 0.5% bupivacaine with 2.5 μg/ml of epinephrine [3]. After each local anesthetic block, the probe of a hand-held cryoneurolysis device (Iovera®, Myoscience, USA) was advanced under ultrasound guidance toward the intercostal nerve, and two 2-minute freeze-thaw cycles were applied to each intercostal nerve (Fig. 1). Over the following 12 hours, the patient’s opioid analgesic requirement decreased precipitously, and she was successfully extubated. The patient remained in the intensive care unit for two additional days, but she did not require re-intubation and her pain was well managed.

**Fig. 1.** Ultrasound-guided percutaneous cryoneurolysis. (A) Parasagittal ultrasound view of T5–T8 intercostal nerves prior to cryoneurolysis, (B) Labeled anatomy of image A, (C) Parasagittal ultrasound view of cryoneurolysis of T7 intercostal nerve, (D) Labeled anatomy of image C. Cyan circle indicates area of ice ball created from cryoneurolysis, white line: trajectory of cryoneurolysis probe.
controlled without opioid analgesics.

Nine days following the cryoneurolysis procedure, the patient's rib fracture pain returned; however, the pain at this time was manageable with oral acetaminophen and extended release lidocaine patches and was not associated with pulmonary compromise.

Case 2

A 64-year-old woman with a history of hypertension and osteoporosis presented with right 4th–8th rib fractures after a fall from standing height. At rest, the patient rated her pain as 3/10; however, this increased to 10/10 with coughing or incentive spirometer (IS) use. The patient was unable to cough due to the pain and had significant difficulty getting out of bed to walk with physical therapy. The patient underwent intercostal cryoneurolysis of the right 4th–8th intercostal nerves (without a local anesthetic nerve block). Two 2-minute freeze-thaw cycles applied to each intercostal nerve using a console cryoneurolysis device (PainBlocker™, Epimed International, USA). Within 1 hour after cryoneurolysis, the patient's pain at rest had decreased to 0/10, her pain with coughing and IS use was rated 3/10, and her IS values increased from 500 ml to 1,500 ml. The patient reported similar pain scores and IS values for the subsequent two days.

Twenty-one days following the cryoneurolysis procedure, the patient noticed an increase in her pain, with her resting pain scores increasing to 3/10 and pain scores during incentive spirometry increasing to 5/10. The pain at this time was easily controllable with oral analgesics.

Case 3

A 73-year-old man with a medical history significant for atrial fibrillation, heart failure, type-II diabetes mellitus, and rectal and thyroid cancer presented with right 3rd–6th rib fractures after a motor vehicle accident. The patient reported a pain score of 6/10 at rest, which increased to 8/10 with IS use and coughing. Cryoneurolysis of the right 3rd–6th intercostal nerves was performed as described above using a console cryoneurolysis device (PainBlocker™, Epimed International, USA). Immediately following the procedure, the patient rated his pain at rest as 0/10, increasing to 6/10 with coughing or IS use. The following day, his resting pain score was rated 3/10, increasing to 7/10 with IS use. The patient's pain was manageable with non-opioid analgesics and he did not report a significant increase in his pain over the following month.

Case 4

A 54-year-old previously healthy man presented to the emergency department approximately three weeks after sustaining left 3rd–11th rib fractures during a fall while rock climbing. At the time of the accident, he underwent a video assisted thoracoscopic surgery with rib plating of the 4th–8th ribs at an outside hospital. The patient continued to have significant pain, 8/10 at rest, 10/10 with IS use or coughing. Intercostal cryoneurolysis was performed as described above using a console cryoneurolysis device (PainBlocker™, Epimed International, USA). Immediately following the procedure, the patient rated his pain at rest as 0/10, increasing to 6/10 with coughing or IS use. The following day, his resting pain score was rated 3/10, increasing to 7/10 with IS use. The patient's pain was manageable with non-opioid analgesics and he did not report a significant increase in his pain over the following month.

Case 5

A 51-year-old previously healthy man presented with fractures of the right 1st–8th ribs and left 1st–6th ribs after an all-terrain vehicle accident. The patient received bilateral T5 paravertebral catheters, which provided excellent analgesia. However, the patient was unable to be weaned from the paravertebral infusions due to extreme pain when the infusions were discontinued. Therefore, intercostal cryoneurolysis was performed, first to the left 2nd–6th intercostal nerves, using a console cryoneurolysis device (PainBlocker™, Epimed International, USA). This resulted in a reduction in the patient's left sided chest pain after discontinuing the left paravertebral infusion from a score of 10/10 at rest to 0/10. On the following day, right sided intercostal cryoneurolysis was performed to the right 4th–7th intercostal nerves. This resulted in the resting pain level decreasing from 8/10 to 1/10 and allowing the patient to cough and use his IS. The following day resting pain scores were 2/10 bilaterally and 7/10 when coughing or using the IS. Fifteen days after the first cryoneurolysis procedure, the patient did note a minor increase in pain. However, his pain did remain controllable with oral analgesics.

Long Term Follow-up

At 3-month follow-up, no adverse events or symptoms of neuropathic pain were reported by any patient.

Discussion

Given the limits on the duration of local anesthetic-based nerve
blocks and the prolonged pain that is associated with rib fractures, ultrasound-guided percutaneous cryoneurolysis of the intercostal nerves may be an excellent adjuvant or substitute for local anesthetic-based nerve blocks. In this case series, cryoneurolysis was able to facilitate extubation and improve incentive spirometry use (decreasing the likelihood of intubation) in patients. Decreased length of intubation or avoidance of intubation is associated with significantly reduced incidence of pulmonary infection [1,6].

The physiological mechanism for cryoneurolysis analgesia is well established and its use relatively common in treating chronic pain. Nerves exposed to extremely cold temperatures exhibit an extended but reversible block. After cryoneurolysis, the neuronal axons undergo Wallerian degeneration distal to the site of treatment [7]. If the entire nerve is adequately treated, the degeneration is consistent across the nerve bundle. Regrowth of axons into the perineurium, which remains intact after cryoneurolysis, eventually restores sensation and the block functionally resolves [8].

As with any therapeutic modality, caution must be used when implementing a new technique. Intercostal local anesthetic-based nerve blocks have an incidence of pneumothorax that may be over 1% [9], and it is reasonable to assume intercostal cryoneurolysis holds a similar risk (although with a more-blunt probe—compared with a sharper needle—the risk may be decreased). Large randomized trials will be required to fully evaluate the risk-benefit ratio of intercostal cryoneurolysis for traumatic rib fractures prior to widespread adoption of the technique.

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Conflicts of Interest

John J. Finneran (Dr. Finneran's institution has received funding and/or product for his research from Myoscience, Epimed, Ferrosan Medical, and SPR Therapeutics)
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Laura N. Godat (Dr. Godat's institution has received product used in this report from Myoscience and Epimed)
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Author Contributions

John Finneran (Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing)
Rodney Gabriel (Conceptualization; Methodology; Writing – review & editing)
Matthew Swisher (Conceptualization; Methodology; Writing – review & editing)
Allison Berndtson (Conceptualization; Methodology; Writing – review & editing)
Laura Godat (Conceptualization; Methodology; Writing – review & editing)
Todd Costantini (Conceptualization; Methodology; Writing – review & editing)
Brian Ilfeld (Conceptualization; Funding; Methodology; Writing – review & editing)

ORCID

John J. Finneran, https://orcid.org/0000-0002-0955-155X
Rodney A. Gabriel, https://orcid.org/0000-0003-4443-0021
Matthew W. Swisher, https://orcid.org/0000-0003-2196-6288
Allison E. Berndtson, https://orcid.org/0000-0002-7299-453X
Laura N. Godat, https://orcid.org/0000-0003-4088-2418
Todd W. Costantini, https://orcid.org/0000-0002-0215-5327
Brian M. Ilfeld, https://orcid.org/0000-0002-6144-3273

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Low thoracic erector spinae plane block for perioperative analgesia in transfeminine bottom surgery

Luis A. Verduzco

Department of Anesthesiology, Denver Health Medical Center, Denver, University of Colorado School of Medicine, Aurora, CO, USA

Approximately 1 million people in the United States are transgender [1]. Transfeminine bottom surgery (TBS) transforms the male genitalia into that of a female; however, the optimal perioperative anesthetic plan remains undetermined. The ultrasound-guided erector spinae plane block (ESP) is an interfascial plane block used primarily for post-operative analgesia [2,3]. It is effective in lumbo-sacral surgery [4], thus suggesting a possible role in TBS. We report the use of an ultrasound-guided ESP block as part of a multi-modal analgesic technique to avoid intra-operative opioids and minimize post-operative opioids. The patient provided informed consent to publish the case.

A 32-year-old woman weighing 70 kg (male by sex) with a history of asthma and gender dysphoria was scheduled to undergo orchiectomy, penectomy, clitoroplasty, labiaplasty, and vaginoplasty. In the preoperative area, she received 1000 mg of oral acetaminophen, 600 mg of oral gabapentin, and a scopolamine patch. Upon entering the operating room, she was given 2 mg of intravenous (IV) midazolam for anxiolysis, and she was sat up. Standard monitors were attached, and her back was sterilely prepped; using a low-frequency curvilinear transducer in parasagittal orientation (rC60xi, SonoSite SII, FUJIFILM SonoSite Inc., USA), the right-sided ribs were counted, starting rostrally at the neck until T11 was located. The probe was moved medially to locate the transverse process (TP). Under ultrasound guidance, a 21 g nerve block needle (SonoPlex STIM, Pajunk Medical Systems L.P., USA) was inserted in-plane rostral to caudal until the TP was contacted (Fig. 1A); after aspiration demonstrated no blood return, a bolus of 35 ml of 0.25% plain bupivacaine mixed with 1 : 200,000 epinephrine was injected through the needle. This was repeated on the left side. The ultrasound was then used to demonstrate lung sliding bilaterally (Fig. 1B), confirming no pneumothorax after the nerve block. The patient was laid back and induced with 70 mg IV lidocaine and 100 mg IV propofol followed by 50 mg IV rocuronium; mask ventilation and intubation proceeded uneventfully.

During the 4-hour surgery, she was maintained on a propofol drip at 75 μg/kg/min and sevoflurane at an end-tidal concentration of 1%; as part of a multi-modal regimen, she received dexamethasone 8 mg IV, ketamine 50 mg IV, dexmedetomidine at 0.3 μg/kg/h (total 71 μg), and esmolol at 35–50 μg/kg/min. No opioids were administered, nor additional local anesthetic injected by the surgeon, and 2200 μg of phenylephrine were required to maintain systolic blood pressures in the high 90s of mmHg 116/77 mmHg.

Extubation was uneventful, and the patient complained of minimal pain, specifically, she stated that she had more “gas pain, than surgical pain,” requiring only 50 μg fentanyl, 30 mg ketorolac, and 5 mg oxycodone in the post anesthesia care unit. Her post-operative pain regimen included acetaminophen 1000 mg orally every 6 hours and ibuprofen 600 mg orally every 6 hours with breakthrough oxycodone (5–10 mg every 3–4 hours when necessary); on postoperative day (POD) 0, she tolerated food and requested 10 mg oxy-
codone in addition to simethicone for gas pain. Unfortunately, the patient developed bleeding from her surgical site and required a return to the operating room early on POD 1 for an exam under general anesthesia, during which she received 2 mg IV midazolam, 50 μg IV fentanyl, and 50 mg IV ketamine. No source was found, and she was re-packed and transferred to the floor. Her consequent hospital course was unremarkable, with the patient repeatedly stating her pain was well controlled. She required only 70 mg oxycodone over the next 2.5 days, after which she was discharged home.

TBS involves sensitive anatomy, and beyond a single published abstract suggesting the use of pudendal nerve blocks for post-operative pain control, guidance relies on opinion [5]. There are no previously published cases demonstrating the efficacy of the ESP block for genital surgery, possibly because the innervation involves sacral nerve roots. We used a high volume of local anesthetic to ensure spread; indeed, the ESP block facilitated the minimization of opioids during hospital stay while still affording excellent pain control.

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**Conflicts of Interest**

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

**References**

Is the mid-transverse process to pleura block a better technique for patients with obesity undergoing modified radical mastectomy?

Rashmi Syal, Rakesh Kumar, Swati Chhabra, Mussavvir Agha
Department of Anesthesiology and Critical Care, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

Obesity in surgical patients presents with numerous challenges for anesthesiologists. Difficult airways, associated comorbidities, and postoperative pulmonary and thromboembolic complications are some of the difficulties encountered. Combining regional blocks with general anesthesia helps overcome many of these difficulties by reducing the opioid requirement and decreasing the incidence of postoperative nausea/vomiting, thus allowing early ambulation [1]. Regional blocks are quite popular and efficacious in the management of pain associated with breast surgeries and form an important component of multimodal pain management. Amongst them, thoracic epidural and thoracic para-vertebral block (TPVB) are most commonly used, but they may be associated with complications, such as accidental dural puncture, epidural abscess/hematoma, spinal cord injury, pneumothorax etc. Moreover, these techniques might be technically difficult in patients with obesity even under ultrasound guidance. In the quest of safer techniques, novel blocks or alternative approaches to existing techniques have been devised to be pain free with minimal inherent risks. One such approach of the paravertebral block has recently been introduced as the “mid-transverse process to pleura” (MTP) block [2].

A 64-year-old woman with morbid obesity, weighing 100 kg (body mass index: 41.66 kg/m²), was scheduled for modified radical mastectomy. She had known hypertension, type II diabetes mellitus, and obstructive sleep apnea. In the block room, the patient was premedicated with intravenous midazolam 1 mg and fentanyl 50 µg. In the sitting position and under sterile conditions, the T4 spine was palpated, and a high-frequency linear ultrasound probe (LOGIQe, GE Healthcare, China) was placed longitudinally, approximately 2.5 cm lateral to the midline. After skin infiltration with a local anesthetic, a 100-mm short-bevel echogenic needle (Contiplex®, B. Braun, Germany) was inserted in-plane from the cranial to the caudal direction. The desired end point for the needle tip was the midpoint of the line between the posterior border of the transverse process and the pleura (Fig. 1A). A titrated bolus of 20 ml of 0.5% ropivacaine was injected at the target site after confirming the spread with 2 ml of normal saline (Fig. 1B). Thereafter, a 20-gauge catheter was threaded through the needle, with the catheter tip placed approximately 3 cm beyond the needle tip. Sensory mapping with a cold swab and pinprick with a 20-gauge needle over the anterior and lateral chest walls revealed a dermatomal block from T1 to T7 30 min after the administration. General anesthesia was induced in accordance with the institutional protocol. Intraoperatively, 0.5% ropivacaine infusion was maintained at 8 ml/h. The hemodynamic parameters were stable throughout the surgical procedure, with no further requirement of opioids after 150 µg of fentanyl administered at the anesthetic induction. Postoperatively, analgesia was maintained with intravenous paracetamol 1 g every 8 h and infusion of 0.2% of ropivacaine at the rate of 8 ml/h in the
The postoperative period up to 72 h. The patient required additional rescue analgesia in the third postoperative hour, which was induced with an injection of diclofenac 75 mg. Overall, postoperatively, her visual analogue scale score at rest and on movement remained in the ranges of 2–3/10 and 3–4/10, respectively, with analgesia maintained with a ropivacaine 0.2% infusion, paracetamol (1 g, 8 hourly), and a single rescue dose of diclofenac, as aforementioned. The patient was extremely satisfied, had ambulatory capacity, and had no pain or nausea/vomiting.

The reduced opioid requirement, decreased incidence of postoperative nausea and vomiting, early ambulation, and better recovery profile made the regional nerve blocks all the more important for multimodal pain management. With an increased use of ultrasound in regional anesthesia, the current trend is to go more peripheral and look for more specific targets depending on the desired outcome; thus, making the fascial and plane blocks more popular. The recently described fascial blocks for thoracic surgeries include the erector spinae plane, retrolaminar, intercostal paraspinal, and MTP blocks. The MTP block, described by Costache et al. [2] is the most recent one. It involves deposition of the drug midway between the transverse process and the pleura. Costache et al. [2] postulated that the local anesthetic deposited at this point may reach the paravertebral space through several possible mechanisms, such as medially through the gap between the superior costotransverse ligament (SCTL) and vertebral bodies, through fenestrations in SCTL, and laterally through the internal intercostal membrane. Syal et al. [3] described the role of this novel technique in a patient with multiple rib fractures with excellent pain relief, while Bhoi et al. [4] reported this block in three patients scheduled for modified radical mastectomy with favorable results. The present patient with morbid obesity was managed safely and successfully with multimodal analgesia with the MTP block. Postoperatively, continuous infusion of 0.2% ropivacaine met the analgesic requirements to a great extent. Only paracetamol was used as an adjunct, and a single rescue dose of diclofenac was required. A reduced opioid requirement was advantageous in avoiding postoperative nausea/vomiting, excessive sedation, respiratory depression, constipation, etc. All this helped the patient achieve early ambulation and recovery. The advantage of the MTP block over the conventional TPVB is that the visualization of SCTL is not required, which might be difficult in patients with obesity. The second advantage is that the target point of the needle is very superficial and far from structures, such as the pleura and neurovascular bundles, making this novel block much safer.

In conclusion, the MTP block is a safe option in patients with obesity scheduled for breast surgery, although well-designed controlled studies are warranted for evaluating the statistical significance.

Conflicts of Interest

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

Author Contributions

Rashmi Syal (Conceptualization; Data curation; Visualization; Writing – original draft; Writing – review & editing)
Rakesh Kumar (Conceptualization; Data curation; Supervision; Writing – original draft; Writing – review & editing)
Swati Chhabra (Conceptualization; Data curation; Resources; Writing – original draft; Writing – review & editing)
Mussavvir Agha (Data curation; Resources; Writing – review & editing)

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Impact of an ultrasound-guided regional anesthesia workshop on participants’ confidence levels and clinical practice

Dong An1, Nicholas D. Black1, Sarah Tierney2, Vincent W.S. Chan1, Ahtsham U. Niazi1

1Department of Anesthesia and Pain Management, Toronto Western Hospital, University of Toronto, Toronto, 2Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, Canada

The use of ultrasound-guided regional anesthesia (UGRA) has increased, leading to a growing demand for UGRA training [1]. Education may be particularly challenging for those already in established practice because educational opportunities are less obvious. In 2009, the American and European Societies of Regional Anesthesia published guidelines for training pathways in UGRA [2]. For practicing anesthesiologists, they recommended workshops consisting of “didactic teaching and hands-on experience” [2]. However, there is limited evidence [3] suggesting that these workshops are effective and can impact participants’ clinical practice. We aimed to assess if attendance at a UGRA workshop improved confidence in block performance and impacted clinical practice.

Since 2004, the regional anesthesia group at Toronto Western Hospital, University Health Network has conducted semi-annual UGRA workshops. These 2-day workshops consist of didactic lectures, live scanning of models under expert supervision, and needling practice on low fidelity simulators. The course curriculum includes teaching on upper and lower limb blocks, truncal blocks, and neuraxial ultrasound. To assess the impact of the workshop, participants were sent an online survey after completion of two courses in 2018.

The primary outcome assessed with our survey was the change in participants’ confidence levels post-workshop. Secondary outcomes included participants’ perceptions on whether or not the workshop made a relevant impact on their clinical practice and to identify the important factors, which can increase the use of UGRA in clinical practice.

Of the 99 people who participated in the two workshops, 58 (59%) responded to the follow-up survey, and 34% of the participants stated that they felt confident in performing UGRA blocks prior to attending the workshop, which increased to 66% after the workshop (P < 0.001; McNemar’s test) (Fig. 1A). The major reason participants said they were not confident was the lack of needling practice (67%). Other common reasons included inadequate scanning practice (20%) and insufficient knowledge of block procedure (13%). For less experienced participants (defined as having previously performed less than 50 blocks), there was a significant increase in the percentage of participants who felt confident after the workshop. The number of confident participants in the less experienced group rose from 6% before the workshop to 61% after (P < 0.001; McNemar’s test) (Fig. 1B). In contrast, more experienced participants (defined as having previously performed more than 50 blocks) showed no change in their confidence levels before and after the workshop (Fig. 1B).

Most (95%) participants stated that the workshop made a relevant impact on their clin-
ical practice. When asked about the most important factor increasing the use of UGRA in their practice, adequate training, adequate time for performing the UGRA blocks, and more surgical procedures were stated by 33%, 19%, and 13% of the participants, respectively. Other factors included buy-in by surgical colleagues (11%), adequate mentorship (9%), refreshment of skillset (7%), refreshment of knowledge (4%), and adequate equipment (4%).

Results of our survey provided evidence for the training recommendations made by the American and European Societies of Regional Anesthesia [2]. The workshops were effective in improving participants’ confidence levels in performing UGRA; however, this was only seen for participants with less experience. A study assessing the impact of an UGRA workshop among anesthesiology residents demonstrated a similar finding [3]. With less previous exposure, it is reasonable that participants with less experience have more to gain. Additionally, most participants stated that the workshop made a relevant impact on their clinical practice. Kim et al. [4] also assessed an UGRA workshop for practicing anesthesiologists, reporting that participants performed more UGRA blocks after the workshop. The subjective findings from our survey offer support that workshop attendance facilitates changes in clinical practice.

Adequate training was the most commonly cited factor increasing the use of UGRA in clinical practice. In a survey by the American Society of Regional Anesthesia and Pain Medicine in 2010, the most frequently cited reason for not practicing UGRA was the lack of training [5]. These findings emphasize on the importance of effective educational tools to facilitate the translation of skills to clinical practice. Few participants stated adequate equipment as a factor increasing their use of UGRA. The study by Kim et al. [4] also demonstrated that available equipment was not a barrier for most practicing anesthesiologists. These findings are in contrast to the 2010 survey, which found that the most difficult challenge to overcome for members was the availability of ultrasound equipment [5]. As such, it is possible that ultrasound equipment is becoming more readily available.

Future work should aim to improve the workshops by investigating the appropriateness of the workshop for physicians with varying degrees of experience. One possibility is to have separate workshops with a more advanced curriculum for trainees with more experience. Another consideration is to make the workshops more flexible in content, catering to the learning needs of the specific participants. In response to our survey, we have started offering advanced UGRA workshops where more complex and novel techniques are taught. The participants are given a chance to choose the blocks that they would like to learn, and each technique is taught via small group learning.

In conclusion, we found support for UGRA workshops targeted at practising physicians. Future work remains to elicit the most effective structure and content of these workshops.

Acknowledgements

The authors would like to thank Rongyu Jin for her help with developing and conducting the survey. Dr. Vincent WS. Chan has received honorarium from Heron Therapeutics.

Conflicts of Interest

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

Author Contributions

Dong An (Formal analysis; Writing – original draft; Writing – review & editing)
Nicholas D. Black (Formal analysis; Writing – original draft; Writing – review & editing)
Sarah Tierney (Conceptualization; Investigation; Methodology; Writing – review & editing)
Vincent W.S. Chan (Conceptualization; Investigation; Methodology; Writing – review & editing)
Ahtsham U. Niazi (Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing)

ORCID
Dong An, https://orcid.org/0000-0002-0062-023X
Nicholas D. Black, https://orcid.org/0000-0001-8580-3897
Sarah Tierney, https://orcid.org/0000-0002-7567-8292
Vincent W.S. Chan, https://orcid.org/0000-0003-0696-708X
Ahtsham U. Niazi, https://orcid.org/0000-0001-6447-4393

References
Retraction: Noninvasive versus invasive ventilation: one modality cannot fit all during COVID-19 outbreak

Abhishek Singh

Department of Anesthesiology Pain Medicine and Critical Care, All India Institute of Medical Sciences, New Delhi, India

The following article from the Korean Journal of Anesthesiology (KJA), "Noninvasive versus invasive ventilation: one modality cannot fit all during COVID-19 outbreak" [1] published on August 2020 has been retracted from publication.

The authors violated the publication ethics by plagiarizing a paper (Online ahead of print; Non-invasive versus invasive ventilation in COVID-19: one size does not fit all!) published in Anesthesia and Analgesia [2]. The arrangement of titles and subtitles match, and there are clearly few changes or additions to the contents, or their expression in papers published in both the journals.

Therefore, the editorial board and publication ethics committee of the KJA decided to retract this paper from our journal. We apologize to readers and try the best to thoroughly screen any plagiarisms and ethics violations prior to the publications of papers submitted and accepted in our journal.

References

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Enacted March 24, 1995
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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.
⁸http://www.amamanualofstyle.com/
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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.

⑥ 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.

⑦ References

· References should be obviously related to documents and should not 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.


Ex) Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth 1996; 77:
441-4.
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.
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.
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 English word should be capitalized.
② Connections between numbers should be denoted by “-”, not “~”. Do not space the numbers (ex. 2–4).
③ Figures (line drawings) should be clearly printed in black and white.
④ Figures should be explained briefly in the footnotes. The format is the same as the table format.
⑤ An individual should not be recognizable in the photographs 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, audio or video files, but also data files should be added here.
Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and be discussed in the text. Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) in the video clips. However, all identifying information, including patient name and/or ID number, hospital name, and date of the procedure, should be removed.
Video clips should contain succinct teaching points that must be supported by the current literature or standard reference texts, preferably those most accessible to the general reader. The adequacy of the teaching points will be evaluated during the review process and finally confirmed by the editorial board at the end of the review process.
Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.
① The video clip(s) should have simple file names (e.g., Video 1***, Video 2*** ) and include the appropriate extension (e.g., mov, mpg).
② The maximum number of video clips is 20.
③ The video clip(s) should be playable on both Windows and MAC computers. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.
④ Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.
⑤ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

2) Case Reports
A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or population, that is so unusual that a clinical trial is not feasible.
Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.
(1) Title page: Same as clinical and experimental studies.
(2) Manuscript
① Title and Running title.
② Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.
③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.
④ Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.
⑤ Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.
⑥ References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board.
⑦ Tables and figures: Proportional to clinical and experimental studies.
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, 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.