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REVIEW

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Regional anesthesia for pediatric cardiac surgery: a review

Burhan Dost[1*], Alessandro De Cassai[2,3], Sara Amaral[4], Eleonora Balzani[5], Yunus Emre Karapinar[6,7], Müzeyyen Beldagli[8], Mirac Selcen Ozkal Yalin[6,7], Esra Turunc[1], Ali Ahiskalioglu[6,7] and Serkan Tulgar[8]

Abstract

Background Effective pain management in pediatric cardiac surgery is essential for optimizing postoperative outcomes and promoting faster recovery. While intravenous analgesia remains a standard approach, regional anesthesia (RA) techniques have gained attention in this population due to their analgesic efficacy, reduced dependence on systemic opioids, and enhanced hemodynamic stability.

Main Body This article provides an overview of current evidence of RA techniques for pediatric cardiac surgery. We discuss the role of RA in pediatric pain management, outlining various techniques, such as epidural, paravertebral block, fascial plane blocks and their specific applications, clinical outcomes, and the challenges posed by pediatric anatomy and pharmacokinetics. Pain assessment in pediatric populations and the complications associated with RA are also explored.

Conclusion Despite the demonstrated efficacy of RA in this patient group, there is a need for large-scale randomized multicenter studies to establish standardized protocols and strengthen the evidence base for its use in pediatric cardiac surgery.

Keywords Children, Cardiac Surgery, Local Anesthesia, Nerve block, Pain

*Correspondence:
Burhan Dost
burhandost@hotmail.com
[1] Department of Anesthesiology and Reanimation, Faculty of Medicine, Ondokuz Mayis University, Samsun TR55139, Türkiye
[2] Institute of Anesthesia and Intensive Care Unit, University Hospital of Padua, Padua, Italy
[3] Department of Medicine - DIMED, University of Padua, Padua, Italy
[4] Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA
[5] Department of Surgical Sciences, University of Turin, Turin, Italy
[6] Department of Anesthesiology and Reanimation, Ataturk University School of Medicine, Erzurum, Türkiye
[7] Clinical Research, Development and Design Application and Research Center, Ataturk University School of Medicine, Erzurum, Türkiye
[8] Department of Anesthesiology and Reanimation, Faculty of Medicine, Samsun Training and Research Hospital, Samsun University, Samsun, Türkiye

Background

Postoperative pain management is a challenge in pediatric cardiac surgery as inadequate pain control is associated with hemodynamic instability, postoperative respiratory complications, prolonged intubation, and prolonged intensive care unit (ICU) and hospital stay [1, 2]. Considering that the main sources of pain after cardiac surgery include sternotomy or thoracotomy incisions [3], efforts are being made to develop more refined and less invasive techniques, with the inclusion of minithoracotomy, ministernotomy and thoracoscopy accesses [4, 5].

Several regional anesthesia (RA) techniques have been proposed for pediatric patients undergoing cardiac surgery, ranging from neuraxial approaches to fascial plane blocks [6]. The Enhanced Recovery After Surgery (ERAS) guidelines emphasize the importance of effective perioperative pain management in improving patient outcomes.

Within this framework, RA techniques are recommended for their opioid-sparing effects in pediatric cardiac surgery [7].

However, the rapid development of these techniques, especially fascial plane blocks, leave room for several uncertainties especially related to the mechanism of action, appropriate type, volume, concentration and pharmacokinetics of local anesthetics (LA). Moreover, most of the studies have been performed on adult patients and it is debatable if they could be transferred to the pediatric population [6, 8, 9].

Therefore, application of RA techniques in pediatric cardiac surgery is complex and continuously evolving; the aim of this review is to summarize the existing knowledge regarding RA for pediatric patients undergoing cardiac surgery outlining their application methods and anatomical underpinnings, supported by illustrative clinical examples to highlight their practical implementation and effectiveness.

Clinical outcomes

RA provides a targeted approach for pain control by interrupting the transmission of pain signals at the site of injury, resulting in more efficient and prolonged pain relief than conventional IV analgesia. In 2023, network meta-analysis of over 5,000 adult patients undergoing cardiac surgery revealed that RA techniques provided superior pain control when compared to conventional IV analgesia [10], similar results were reported for pediatric patients, even if the total population of the meta-analysis comprised only 605 children from 14 RCTs [11].

Targeted approaches of regional techniques facilitate effective pain management and reduce the need for systemic opioids, thereby decreasing the associated side effects [12]. Ineffective postoperative pain management leads to chronic pain, immunosuppression, infections, and impaired wound healing [13, 14]. Moreover, uncontrolled pain in children can lead to both immediate and long-term consequences, including heightened anxiety and potential behavioral disturbances [15].

Traditionally, IV analgesia is used as the primary method for pain control; however, it is associated with adverse effects that can prolong the ICU and hospital stay of the patients [16]. RA is increasingly used for pediatric cardiac surgery in hopes it will enhance the clinical outcomes and reduce complications [17]. Neuraxial techniques, such as the epidural technique, suppress the inflammatory response and sympathetic activity, which is crucial for patients as extracorporeal circulation, hypothermia, and surgical stress exacerbate the inflammatory response [18]. RA reduces opioid consumption and pain score via effective postoperative pain relief [19, 20], thereby decreasing the incidence of opioid-induced respiratory depression and other adverse events, such as gastrointestinal disturbances, pruritus, opioid hypersensitivity, and oversedation, which complicate postoperative treatment and prolong recovery [21, 22].

Prolonged ICU and hospital stay poses a significant burden on patients and their families, especially on pediatric patients as being away from their parents significantly influences their motivation and cooperation with subsequent treatment [23]. Additionally, pediatric patients exhibit the most intense negative psychological and behavioral outcomes following critical illness and prolonged ICU stay [24]. Prolonged stay also imposes a significant financial strain on healthcare systems due to the need for intensive care and related treatments. Effective pain management alleviates these social and economic burdens while improving patient outcomes [25].

Pain assessment

In pediatric cardiac surgery, assessing pain during intensive care follow-up is challenging due to the difficulty of using self-reported tests; therefore, behavioral observation becomes critical. Tools, such as the Face, Legs, Activity, Cry, and Consolability scale and Modified Objective Pain Scale, rely on observing physical signs of distress, such as facial expressions, body movements, crying, and the ability to be comforted [26]. These tools are especially useful for infants and younger children who cannot verbalize their pain and older children with severe illnesses, which limit self-reporting. However, interpreting child behavior is another challenge. Pain behaviors of children are impacted by fear, anxiety, fatigue, and prior experience, complicating their assessment. Moreover, personal bias and cultural background of the observer also influences the interpretation of patient behaviors [27]. Therefore, physiological measures provide another avenue for pain assessment, relying on objective indicators, such as changes in heart rate, blood pressure, and respiratory rate [28]. However, physiological responses are not specific to pain and can be triggered by other factors, such as stress and illness. Therefore, physiological data combined with self-reports and behavioral observations should be used for accurate assessment [29].

Central neuraxial techniques

Central neuraxial techniques, including spinal [30, 31], caudal [32], and epidural [33] techniques, are used for analgesia during pediatric cardiac surgery. These techniques have demonstrated significant benefits in perioperative pain control. However, their application can cause potential complications, such as epidural hematoma, especially in patients receiving anticoagulation therapy, and unpredictable spread of LAs [34].

Epidural analgesia (EA) remains a cornerstone technique in this context involving the injection of LAs, often combined with opioids, into the epidural space. Beyond its potent analgesic properties, EA also modulates the stress response via sympathetic blockade, stabilizing the hemodynamics during surgery by reducing catecholamine release. This is especially beneficial for pediatric patients, as controlling the body response to surgical stress is critical for maintaining cardiovascular stability in these patients [35].

Paravertebral Block

Paravertebral Block (PVB) involves injecting the LAs near the spinal nerves as they exit the intervertebral foramina, targeting the paravertebral space. Ultrasound guidance reduces the risk of complications, such as pleural puncture. Unlike those of EA, effects of PVB are more localized, resulting in fewer systemic effects, especially on hemodynamic stability. Therefore, PVB is a safe option for children with cardiovascular compromise [36].

Fascial Plane Blocks

Erector spinae plane (ESP) block

ESP block, first described by Forero et al. [37], is an emerging fascial plane block in which LAs are injected into the fascial plane between the erector spinae muscles and thoracic transverse processes (Fig. 1). Although the specific mechanism of ESP block is still under debate [38], the most likely mechanism is that the administered LA spreads in the craniocaudal direction and into the paravertebral area, blocking the dorsal and ventral rami of the spinal nerves and sympathetic ganglia, facilitating both somatic and visceral sensory blockade. When applied bilaterally, ESP block effectively provides analgesia across specific dermatomes, particularly in the T2–7 regions, thereby covering the entire thorax, however the debase is still ongoing as some cadaveric studies suggests the staining of ventral rami could not be constant [39]. Many studies have demonstrated the efficiency of the ESP block for pediatric cardiac surgery. In an RCT by Gado et al., postoperative opioid consumption and pain scores in the first 24 h were significantly lower in pediatric patients with ESP block than in those without ESP block [40]. Another study reported that bilateral ESP

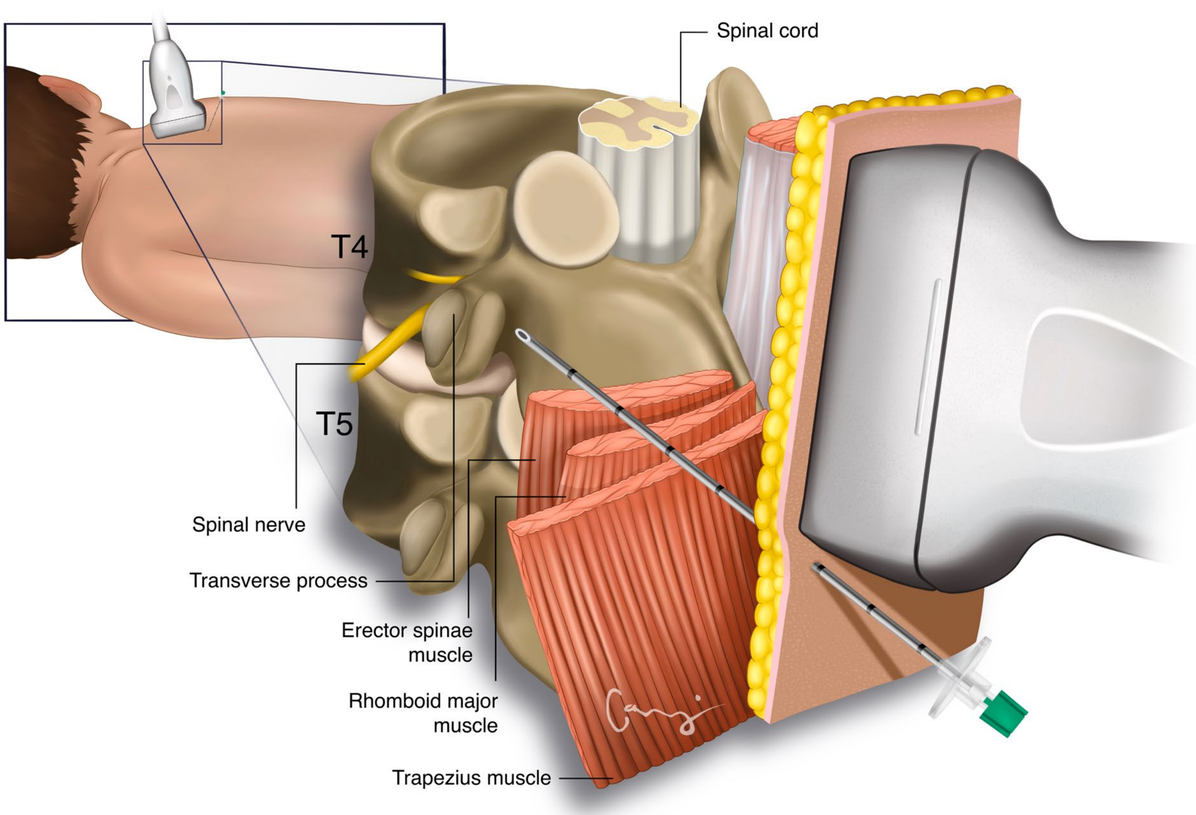

Fig. 1 Schematic illustration of an ultrasound-guided erector spinae plane block

block effectively relieves sternotomy pain, requiring less rescue analgesia and exerting long-lasting effects in the postoperative period [41]. Gustavo et al. compared an ESP block performed at the T5 level with traditional IV opioids and reported that the ESP block was associated with a shorter ICU stay, lower opioid consumption, and faster discharge from the ICU [42].

A systematic review and meta-analysis of five studies, including 384 pediatric cardiac patients—178 of whom received an ESP block—demonstrated notable benefits compared to IV opioid-based analgesia. The analysis revealed that the ESP block significantly reduced intraoperative fentanyl consumption and ICU length of stay in children undergoing cardiac surgery via midline sternotomy. This meta-analysis highlights the potential of the ESP block as a valuable adjunct to existing multimodal analgesia protocols [43].

Mid-transverse process to pleura block (MTPB) and retrolaminar block (RLB)

MTPB and RLB are two variants with a supposed mechanism of action similar to the ESP block (Fig. 2). They work as the LA spreads through the paravertebral space, simultaneously blocking the spinal nerve roots of the ventral and dorsal rami, as the intercostal nerve is blocked at a level not far from the spinal cord [44]. A cadaveric study demonstrated the extensive spread of MTPB into the paravertebral space, ESP, dorsal and ventral rami of the spinal nerves, sympathetic chain, and intercostal nerves [45]. The injection was targeted midway between the transverse process of the thoracic vertebra and pleura, posterior to the superior costotransverse ligament, causing pleural displacement and spreading into the ESP. Abdelbaser et al. [46] reported that MTPB significantly reduces intraoperative fentanyl consumption by blunting the stress response to various surgical stimuli during pediatric cardiac surgery. Moreover, MTPB significantly reduces the extubation time and duration of ICU stay, thereby decreasing the pain score. Another RCT revealed no significant differences in intraoperative hemodynamics, intraoperative fentanyl consumption, 24-h postoperative fentanyl consumption, postoperative pain score, extubation time, and ICU discharge time between the PVB and MTPB groups, with significantly shorter time required to perform bilateral MTPB than for PVB [47].

RLB is another fascial plane block that involves LA injection between the posterior surface of the thoracic vertebral lamina and overlying paraspinal muscles [48]. ESP block targets the tips of transverse processes, whereas RLB targets the laminae [44]. Spread of LA into

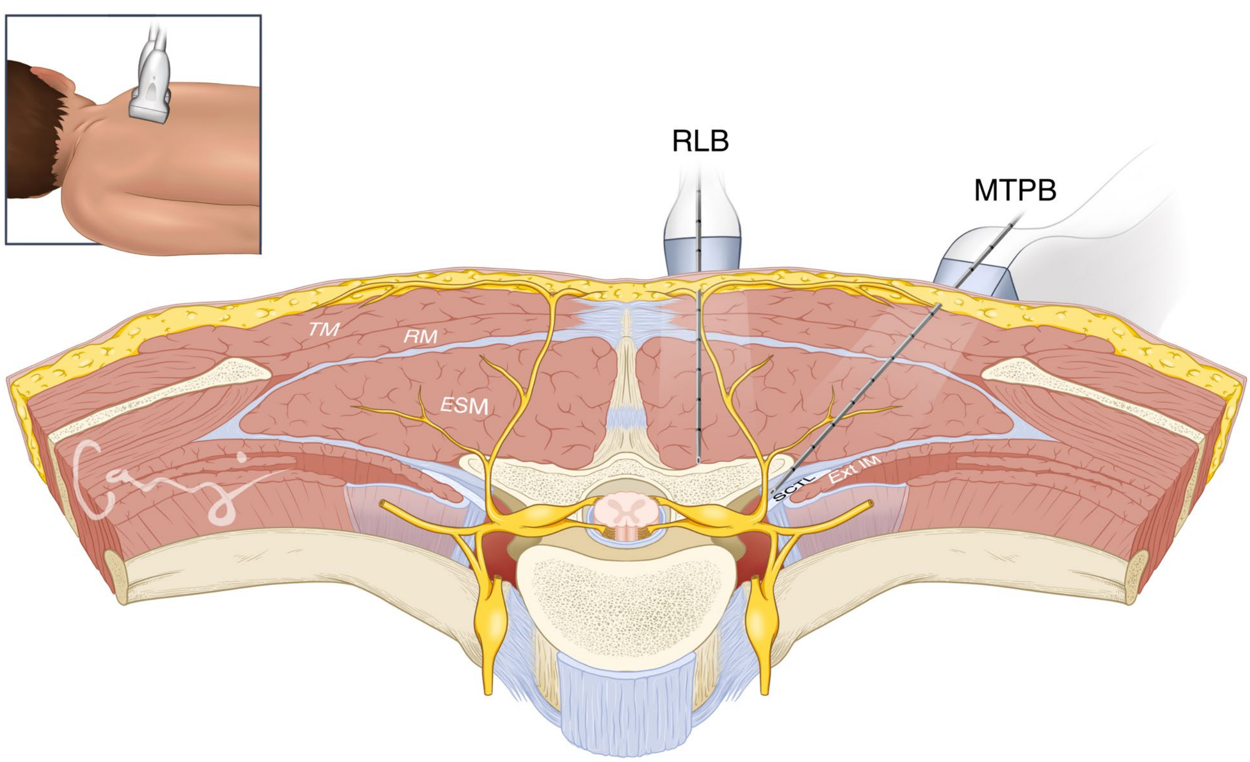

Fig. 2 Schematic illustration of the mid- transverse process to pleura and the retrolaminar block (MTPB is shown in the transverse plane for illustrative purposes; it can be better illustrated in the coronal plane between the two transverse processes.)

the paravertebral and epidural spaces blocks the ventral and dorsal rami of the thoracic spinal nerves and extends laterally into the fascial plane to block the lateral cutaneous branches of intercostal nerves [49]. The potential superiority of RLB over ESP block is probably due to the deeper deposition that may facilitate more consistent diffusion of the LA toward the nerve roots and paravertebral spaces, areas critical for achieving effective somatic and visceral analgesia. A recent network meta-analysis which assessed the RA techniques in pediatric cardiothoracic surgery reported that the largest opioid consumption decrease was in RLB [50].

Ultrasound-guided RLB is theoretically safer than thoracic EA and PVB, as the block needle is inserted away from the pleura and dura [51]. Moreover, no major vessels or nerves exist along the needle path, with only a slight risk of intramuscular hemorrhage [52]. RLB is associated with early extubation and short ICU stay due to the reduction in perioperative opioid consumption after open cardiac surgery via median sternotomy [51].

Interpectoral plane (IPP) and IPP + pectoserratus plane (PSP) blocks

IPP (previously known as PECS-I) block was first described by Blanco in 2011 while IPP + PSP (previously known as PECS-II) block was introduced the following year [53–55]. IPP block involves a single injection of the LA between the pectoralis major and minor muscles, whereas the IPP + PSP block involves an additional injection into the plane between the pectoralis minor and serratus anterior muscles (SAMs) (Fig. 3). IPP block targets the pectoral nerves and possibly the intercostal nerves depending on the injection site, whereas the IPP + PSP block targets the long thoracic, thoracodorsal, and lateral branches of the intercostal nerves.

Although the IPP block is widely used in other context such as breast surgery, its use for cardiac surgery, particularly in pediatric populations, is still in its early stages. To date, most studies have focused on adult populations, leading to insufficient data on pediatric patients, for this reason authors would recommend caution to readers while implementing these techniques in their clinical practice until further evidence is provided by future studies on the topic. Zachary et al. retrospectively evaluated the use of IPP and IPP + PSP blocks for postoperative pain management following sternotomy in 73 pediatric patients. IPP was performed in 47 patients and IPP + PSP in 26 patients. Notably, 34% of patients did not experience severe pain within the first 24 h post-surgery [56]. IPP + PSP block decreases the pain score, opioid consumption, and agitation score [57]. In a retrospective study conducted by Yang et al. in pediatric patients undergoing pacemaker or defibrillator implantation, IPP + PSP block yielded positive outcomes by decreasing the pain score and opioid requirement [58]. IPP and IPP + PSP blocks are more suitable for minimally invasive surgeries, such as pacemaker and defibrillator placement, than anterior mediastinotomy.

Serratus anterior plane (SAP) block

SAP block is performed more laterally and posteriorly than the interpectoral block in the axillary region at the level of the fourth or fifth rib. In this block, LA is injected either between the serratus anterior and latissimus dorsi muscles or beneath the SAMs (Fig. 4). Depending on whether the injection is deep or superficial, different nerve branches are affected: LA injected deep into the SAM blocks the lateral cutaneous branches of the intercostal nerves, whereas a superficial injection blocks the long thoracic and thoracodorsal nerves and lateral cutaneous branch of the intercostal nerve [59]. SAP block spreads across the T2–9 levels, covering the anterior, lateral, and posterior chest walls. Specifically, SAP block provides effective and safe analgesia during the initial hours of the postoperative period [60, 61]. Therefore, SAP block is more feasible for minimally invasive procedures, specifically for cardiac surgeries involving lateral thoracic incisions. A recent study comparing the efficacy of SAP block, IPP + PSP block, and intercostal nerve block for the management of postoperative thoracotomy pain in pediatric cardiac surgery revealed that while the early postoperative pain scores were comparable across all three groups, the SAP block group showed significantly lower pain scores at 6, 8, 10, and 12 h post-extubation compared to the intercostal nerve block group [62]. These results suggest that SAP block may offer a more sustained analgesic effect compared to intercostal nerve block, with a comparable safety profile, making it a promising option for postoperative pain management in pediatric cardiac surgery.

Parasternal intercostal plane (PIP) block

Blocking the anterior cutaneous branches of the thoracic nerve is important for effective pain management after pediatric cardiac surgery [63]. As an alternative to central blocks, targeting the terminal branches innervating the median sternotomy area via direct blockade offers a viable approach to control this specific type of pain [34, 64]. Superficial and deep parasternal intercostal blocks, previously known as pecto-intercostal fascial and transversus thoracic plane blocks, respectively, are increasingly recognized as effective RA techniques for pediatric cardiac surgery, particularly for managing the anterior thoracic wall pain [65, 66].

Superficial-PIP (S-PIP) block, a fascial block that provides analgesia in the parasternal region, decreases opioid

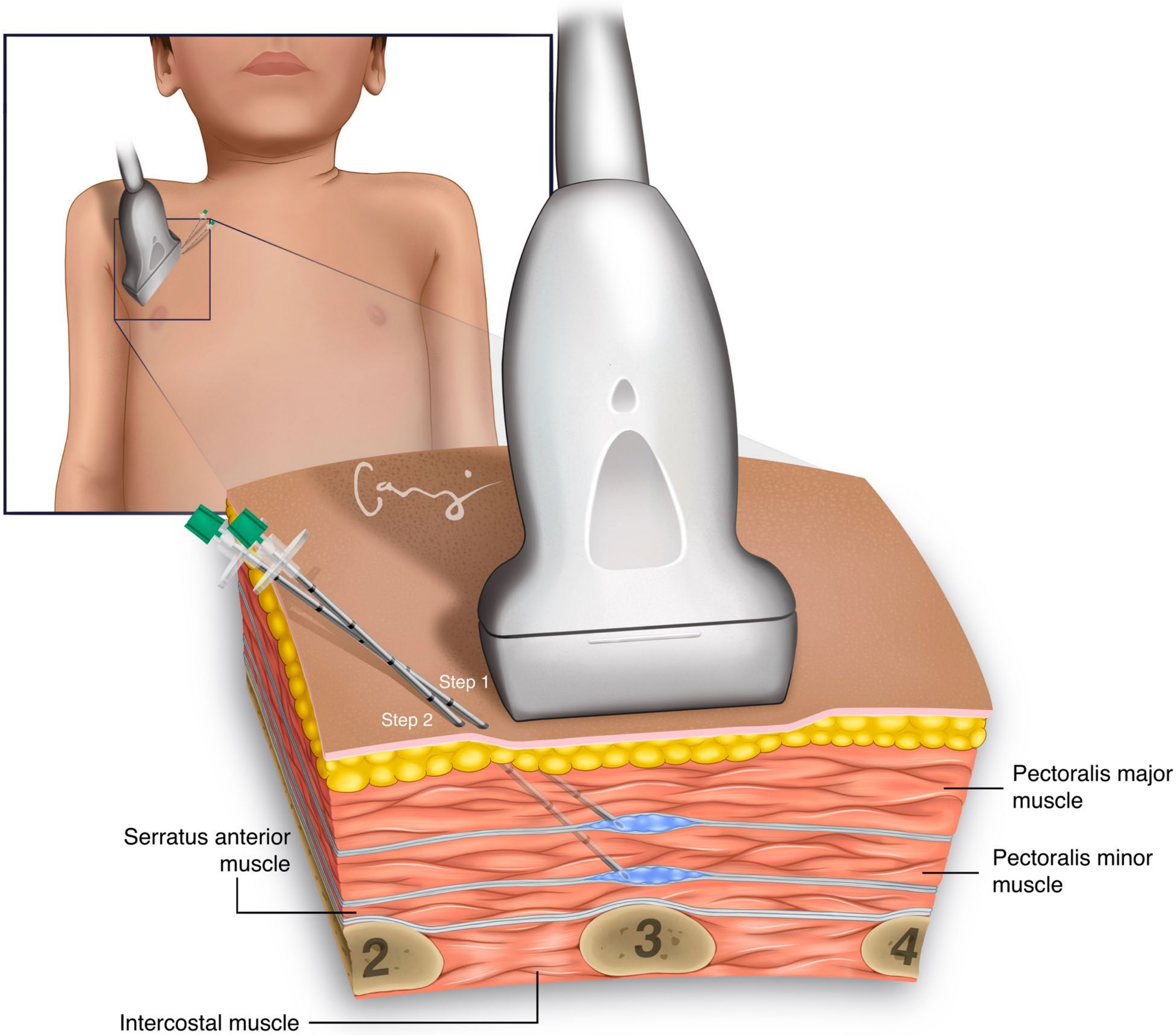

Fig. 3 Schematic illustration of the injection sites for local anesthetic during ultrasound-guided interpectoral and interpectoral-pectoserratus plane blocks. In the interpectoral block, the local anesthetic is injected between the pectoralis major and pectoralis minor muscles. In the interpectoral-pectoserratus plane block, local anesthetic is first injected between the pectoralis major and minor muscles (step 1), and then between the pectoralis minor and serratus anterior muscles (step 2)

consumption following median sternotomy by targeting the anterior cutaneous branches of the thoracic intercostal nerves (Th2–6). In this technique, LA is injected into the fascial plane between the pectoralis major and internal intercostal muscles (Fig. 5). By effectively managing the somatic pain at the incision site, S-PIP minimizes the requirement for systemic opioids. This is particularly beneficial for pediatric patients susceptible to opioid-related side effects, including nausea and pruritus [65]. Deep-PIP (D-PIP) block, which involves the injection of LA between the internal intercostal and transversus thoracic muscles, targets the anterior branches of the intercostal nerves (Fig. 4). Although similar analgesic efficacy of both techniques has been demonstrated in adult patients [67], to date, no study has compared their effects in pediatric populations. Although cadaveric studies [68, 69] suggest the need for multiple injections for the parasternal block, this remains a topic of ongoing debate [70, 71]. Future studies on dermatomes are necessary to provide definitive conclusions.

A systematic review and meta-analysis of six studies including 601 pediatric patients revealed that D-PIP

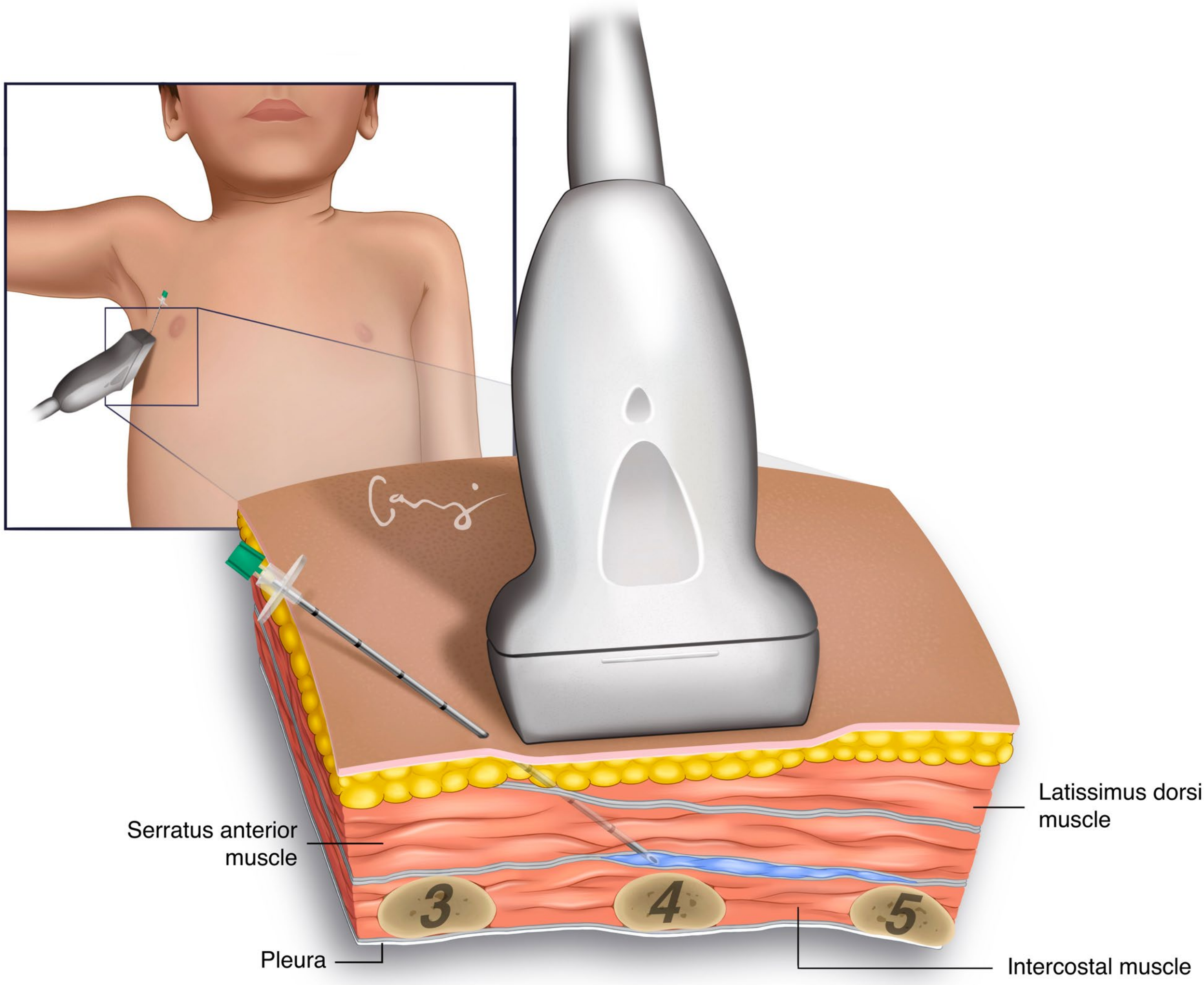

Fig. 4 Schematic illustration of the injection site for local anesthetic during a serratus anterior plane block, with local anesthetic spread (blue areas) between the serratus anterior muscle and the intercostal muscles

block was associated with a reduction in postoperative modified objective pain scores at 12 h, intraoperative opioid consumption, and postoperative opioid consumption with low evidence. These findings highlight the potential clinical utility of D-PIP as a part of multimodal analgesia strategies in pediatric cardiac surgery [66].

Although complications are minimized when analgesic techniques are performed under ultrasound guidance, it is important to emphasize that the D-PIP block has not been validated for use in pediatric patients and carries significant risks. Notably, the risk of pneumothorax and the potential for injury to the internal thoracic artery represent critical challenges to its application. Due to the close proximity of the internal thoracic artery and the severe consequences that may arise from its injury, the D-PIP block should be considered only as an advanced technique and approached with extreme caution, particularly in pediatric settings [72].

In summary, both the S-PIP and D-PIP blocks are effective alternatives to other regional techniques for pediatric cardiac surgery. They offer targeted analgesia for anterior thoracic pain with a favorable safety profile, making them well-suited for pediatric patients.

The block characteristics are summarized in Table 1, highlighting key distinctions in technique, anatomical targets, and clinical applications of the regional techniques.

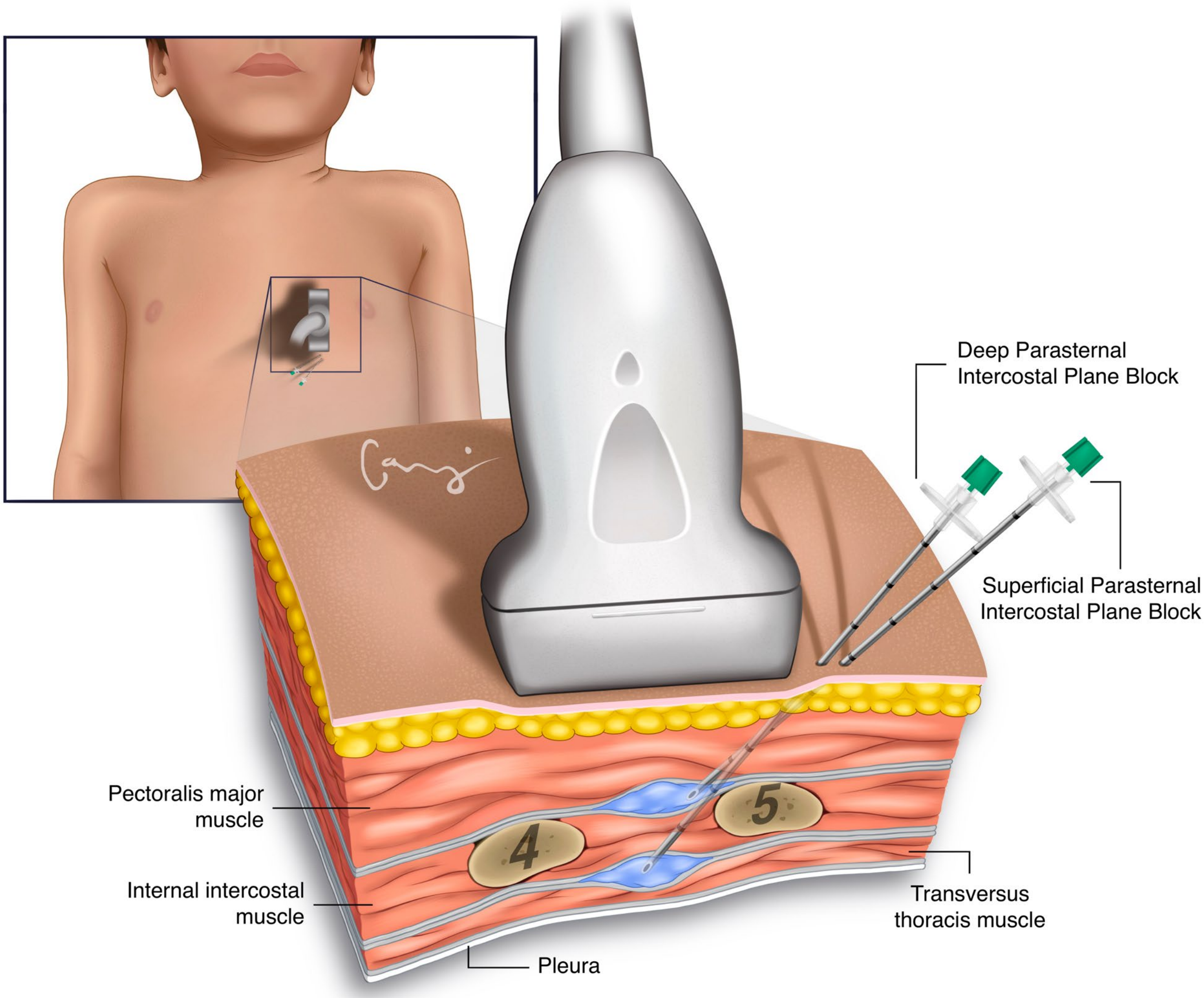

Fig. 5 Schematic illustration of the injection sites for local anesthetic during ultrasound-guided superficial and deep parasternal intercostal plane blocks. The blue highlighted area indicates the desired spread of the local anesthetic

Current challenges and complications

RA poses inherent risks in pediatric patients undergoing cardiac surgery. Although not specifically developed for cardiac surgery, the European Society of Regional Anesthesia has published many documents on the application of RA for the pediatric population [73]. As RA is typically administered while the patient is under general anesthesia, its administration presents unique challenges. Specifically, lack of active participation by the patient and inability to observe the warning signs that an awake patient can exhibit necessitate heightened vigilance for the observation of indirect indicators of LA toxicity. Therefore, every LA injection should be administered in small aliquots (0.1–0.2 mL/kg), with intermittent aspiration and careful monitoring for any changes in the T wave, heart rate, and blood pressure in the immediate minutes following the injection. Any alterations in these parameters should raise the suspicion of intravascular injection until otherwise proven [74].

Determining a one-size-fits-all dosing regimen is challenging as each block exhibits a distinct pharmacokinetic profile. Fascial blocks are characterized by rapid absorption [75], necessitating careful dosing regimens considering the higher distribution volume and different protein assets in infants and children compared to those in adult patients [76, 77]. Therefore, the lowest possible volume and effective concentration should be used for the pediatric population, adhering to the recommended maximum LA dose per kilogram. The concentrations, main benefits, and disadvantages

Table 1 Regional Anesthesia Techniques for Pediatric Cardiac Surgery: Indications, Advantages, and Considerations

Technique	Indications	Advantages	Pediatric-Specific Considerations	Pain Target
Central Neuraxial Techniques	Median sternotomy, thoracotomy	Comprehensive analgesia, modulates stress response, reduces systemic opioid requirements	Contraindicated in anticoagulated patients due to the risk of epidural hematoma	Somatic and visceral pain
Erector Spinae Plane Block	Median sternotomy, thoracotomy	Easy to perform, reduces opioid consumption, shortens ICU stay	Demonstrates a reduction in ICU length of stay and intraoperative fentanyl requirements. Safe and effective in pediatrics	Mechanism of action is unclear, ventral ramus spread is limited
Mid-Transverse Process to Pleura Block & Retrolaminar Block	Median sternotomy, thoracic procedures	Attenuates perioperative stress, shortens extubation time and ICU duration	Limited pediatric evidence, but shows faster recovery and reduced opioid use	Pain from sternotomy or anterior thoracic incisions
Interpectoral + Pectoserratus Plane Blocks	Pacemaker/defibrillator placement, minimally invasive cardiac surgeries	Effective for anterior and lateral thoracic wall pain; reduces agitation scores and opioid requirements	Sparse pediatric data. Potentially effective for minimally invasive chest procedures	Anterior and lateral chest wall pain in the upper thoracic region
Serratus Anterior Plane Block	Lateral thoracic incisions, minimally invasive procedures	Effective for lateral thoracic wall pain	Limited pediatric data	Lateral pain associated with thoracic incisions or chest drain placement
Superficial Parasternal Intercostal Plane Block & Deep Parasternal Intercostal Plane Block	Median sternotomy, pericardiocentesis	Targets anterior thoracic wall pain, reduces systemic opioid use	Low-certainty evidence in pediatrics. Risk of pleural and internal thoracic artery puncture for Deep Parasternal Intercostal Plane Block	Anterior pain related to sternotomy

Abbreviations: ICU Intensive Care Unit

Table 2 Concentrations, Main Benefits, and Disadvantages of Local Anesthetics in Pediatric Cardiac Surgery

Drug	Concentration	Main Benefits	Main Disadvantages
Bupivacaine	0.2 – 0.25%	Longer duration of action	Higher risk of cardiotoxicity and myotoxicity
Ropivacaine		Safer profile	
Volume used	For epidural analgesia; 0.3 mL/kg (thoracic epidural initial loading) and 0.25 mL/kg for subsequent top-up Single injection fascial plane blocks; Bupivacaine or ropivacaine 0.25 to 0.75 mg/kg Continuous infusion for fascial plane block; 0.2% ropivacaine or bupivacaine using an infusion dose of 0.1 to 0.3 mg/kg per hour		
Adjuvants	There is a paucity of studies investigating the use of adjuvants in the pediatric population, with no specific research focusing on their application in pediatric cardiac patients		
Pharmacokinetics	Children's unique physiological characteristics result in a reduced minimum anesthetic concentration required to achieve nerve conduction block. They have a higher proportion of body water and lower levels of plasma binding proteins compared to adults, which influences the pharmacokinetics of local anesthetics. Additionally, their thinner myelin sheaths, smaller nerve diameters, and shorter internodal distances contribute to the effectiveness of blocks at lower local anesthetic concentrations than those needed for adults. However, these same factors increase their susceptibility to local anesthetic systemic toxicity, necessitating strict adherence to maximum dosage guidelines to ensure safety		

of LA used in pediatric cardiac surgery are presented in Table 2 [73, 76, 78–81]. Adhering to these limits helps minimize the risk of systemic toxicity, which is crucial given the potential for severe adverse effects such as cardiac arrhythmias and central nervous system disturbances. However, the lack of pharmacokinetic data impairs the recommendations for dose (both bolus and infusion) in children. Until sufficient pharmacokinetic studies are available to establish the optimal dosing regimens for each RA technique, clinicians must prioritize safety by meticulously calculating doses based on patient weight and closely monitoring for signs of LA toxicity.

While adult and pediatric populations share some anatomical and procedural similarities, the clinical evidence base for RA in pediatric cardiac surgery is notably smaller. It is therefore critical to distinguish between findings from adult studies and those specific to pediatric populations, ensuring that evidence is not extrapolated without careful consideration.

Conclusions

Although RA is widely used in multimodal analgesia for pediatric cardiac surgery, high-quality studies on its efficiency are scarce, limiting robust evidence supporting its use. However, recent advancements, such as expanding anatomical knowledge and increasing use of ultrasonography-guided fascial plane blocks, have enhanced its application. Current shift toward opioid-sparing techniques with multimodal analgesia marks the growing demand for fast-track cardiac surgery. In such surgeries, RA plays a crucial role for enhanced recovery by facilitating early extubation and decreasing the hospital stay duration. However, further large-scale randomized multicenter studies are essential to standardize the application of RA in pediatric cardiac surgery and provide robust evidence for its safe and effective use for the pediatric population.

Abbreviations

D-PIP	Deep-parasternal intercostal plane
EA	Epidural analgesia
ERAS	Enhanced Recovery After Surgery
ESP	Erector spinae plane
ICU	Intensive care unit
IPP	Interpectoral plane
IV	Intravenous
LA	Local anesthetic
MTPB	Mid-transverse process to pleura block
PIP	Parasternal intercostal plane
PSP	Pectoserratus plane
PVB	Paravertebral block
RA	Regional anesthesia
RCT	Randomized controlled trial
RLB	Retrolaminar block
S-PIP	Superficial-parasternal intercostal plane
SAM	Serratus anterior muscle
SAP	Serratus anterior plane

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Authors' contributions
Conceptualization, B.D. and A.A.; methodology, A.D.C, S.A., Y.E.K. and E.B.; investigation, E.T., M.B. A.A., S.T., Y.E.K., M.S.O.Y., B.D. and A.A.; resources, B.D.; data curation, E.T., B.D. and A.A.; writing—original draft preparation, B.D., A.A., E.B., S.A., E.T., M.B., A.A., S.T., Y.E.K., and M.S.O.Y.; writing—review and editing, B.D., A.A., E.B., S.A., E.T., M.B., A.A., S.T., Y.E.K., and M.S.O.Y.; project administration, B.D. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
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