Regional anaesthesia in children: an update

Bosenberg AT, MBChB, FFA(SA)
Professor, Department Anesthesiology and Pain Management, Faculty Health Sciences
University of Washington, Seattle Children's Hospital, Seattle, Washington, USA
Correspondence to: Adrian Bosenberg, e-mail: adrian.bosenberg@seattlechildrens.org
Keywords: regional anaesthesia, paediatric, outcomes, maxillary nerve, lumbar plexus, TAP block, clonidine, ketamine

Abstract

Regional anaesthesia for children continues to grow in popularity. The potential benefits of regional anaesthesia over more conventional methods are well recognised, but the level of evidence is small since there are few well designed randomised controlled studies on infants or children. Practice patterns have changed over the past decade. Peripheral nerve blocks are increasingly more favoured than neuraxial blocks. This change has been fuelled by the lower reported incidence of complications associated with peripheral nerve blocks, and is also in keeping with the increase in laparoscopic and thoracoscopic surgery. There has been renewed interest in children following recently described transversus abdominis plane, maxillary nerve and lumbar plexus blocks. The analgesic effect of a "single-shot" block is limited to approximately five hours, irrespective of whether or not bupivacaine, ropivacaine or levobupivacaine are used. Peripheral nerve catheters and adjuvants are two options that are used to prolong the duration of analgesia. Clonidine and ketamine have essentially replaced opiates as the most popular adjuvant in many institutions. Technological advancements are likely to make regional anaesthesia both safer and easier to perform in the future.

 South Afr J Anaesth Analg 2013;19(6):282-288

Introduction

Worldwide paediatric regional anaesthesia continues to evolve. In some countries, regional anaesthesia forms part of the anaesthetic culture, and it is almost expected that analgesia is provided for children after surgery. The use of regional anaesthesia in children remains limited in some institutions because of the perception that the advantages of regional anaesthesia over opiate analgesia[1,2] are not worth the potential risks. Although different, the incidence of risk associated with regional anaesthesia is remarkably similar to that of opiate analgesia, i.e. approximately one per 1 000, based on recent multicentre surveys.[3,4]

When choosing regional anaesthesia, the risks and benefits of any technique must be weighed against the risks and benefits of other forms of analgesia. Many factors influence the choice of technique, and include the age and general condition of the patient, the severity and site of the pain, informed consent, the skill of the provider, and whether or not any contraindication to regional anaesthesia exists. In making the choice, the anaesthesiologist should also take into account availability of the equipment, facilities and the level of available monitoring and nursing care.[2] In general terms, a peripheral nerve block is considered to be safer than a neuraxial block.

Benefits

Untreated pain has several deleterious effects, whereas effective pain relief may play an important role in surgical outcome. Regional anaesthesia is almost universally employed to provide analgesia, but it may also be used for its autonomic and motor effects in special circumstances. Surgical stress, if untreated, produces a spectrum of autonomic, hormonal, metabolic, immunological or inflammatory, and neurobehavioural consequences. Regional anaesthesia is most effective in obtunding this response.

It is difficult to show clear, evidence-based benefits of regional anaesthesia over those pertaining to other forms of analgesia.[1,3-8] With respect to the pyramid of evidence, apart from many single-institution case series, retrospective reviews and anecdotal reports, few prospective randomised control studies have compared regional with general anaesthesia or systemic analgesics in children.[2] Those

that have been performed are often underpowered, have different and varying end-points, and are usually from single institutions. Another confounding factor is that more surgery is being carried out laparoscopically or thoracoscopically, requiring a different analgesic technique than open laparotomy or thoracotomy.[9-12]

Bearing this in mind, there is some evidence to suggest that the benefits of regional anaesthesia in children include haemodynamic stability and a reduction in minimum alveolar concentration, less need for muscle relaxants, the absence of respiratory depression with some evidence of respiratory stimulation, less need for postoperative ventilatory support after major surgery (particularly thoracotomy), an earlier return of gut function and subsequent feeding, enhanced suppression of the metabolic stress response and less immunodepression, in addition to the economic benefits of a shorter intensive care unit and hospital stay.[1,2]

Education

Success in regional blockade involves placing "the right dose of the right drug in the right place".[12] To achieve this goal, individual practitioners require sufficient education and training to acquire the confidence to practise independently.

Anatomy remains the foundation on which regional anaesthesia is built. Paediatric anatomy is somewhat different from adults, and evolves as the child grows.[13] On the positive side, most nerves are superficial and can therefore be better defined with high-frequency ultrasound. Nerve mapping is also easier for practitioners who are restricted to nerve stimulation when nerves are superficial.[14] While ultrasound guidance has virtually become the standard of care in the developed world, nerve stimulation still has its place. After all, not so long ago peripheral nerve stimulators were regarded a major advance, both as a teaching aid and as a means of improving the success rate of peripheral nerve blocks.[14,15]

An understanding of anatomy, pattern recognition, hand-eye coordination and optimal needle visualisation remains the hallmark of safe ultrasound-guided practice. To perform an ultrasound-guided block depends primarily on the operator's ability to locate the nerve, to follow and advance the needle tip towards the target nerve, and to a lesser extent, on the available ultrasound equipment and needle. As the use of ultrasound expands, the best method of teaching is worth considering.

To date, training in ultrasound-guided nerve blocks has not been standardised.[16] Guidelines have been suggested, but most are aimed at practice for adults.[16-24] The role of phantoms in teaching ultrasound-guided regional anaesthesia has recently been reviewed.[21] Simulation of needle control on phantoms is popular and cost-effective, without risk to patients. But they are not ideal since lack of background echogenicity greatly enhances needle visibility that does not resemble the clinical situation.[21] Animal models and fresh frozen cadavres are expensive, but are more realistic.[21] However, the use of paediatric cadavres is not an option. The plethora of workshops that have become available are mainly adult orientated and invariably offer the basics only. Time allocated for individual hands-on experience is usually limited and seldom involves needle insertion into live models.

The ideal is experience gained clinically under expert guidance. These opportunities remain limited to a minority of institutions worldwide. In the author's opinion, the suggested need for ultrasound certification should not become a requirement unless there is real evidence that ultrasound-guided blocks are truly safer than nerve stimulator techniques.

Quality improvement

In this era of evidence-based medicine, coupled with clinical practice that is becoming increasingly risk averse,[2] quality improvement and the safety of regional anaesthesia should be an important focus, both now and in the future. Should regional anaesthesia remain the domain of enthusiasts, or should it be more widely adopted and become standard practice? This remains a topic for debate. Regional anaesthesia clearly has wide-ranging benefits,[1] but requires technical expertise that is still not universally taught.[16-20]

A review of four large prospective multicentre surveys, two from the *Association Des Anesthésistes Réanimateurs Pédiatriques d'Expression Française (ADARPEF)* (Association of French Speaking Paediatric Anaesthetists) that are representative of two different eras,[25,26] one from the UK,[3] and more recently from the Pediatric Regional Anesthesia Network (PRAN) in the USA,[10,11,27] show a remarkable similar incidence of non-life-threatening complications. The initial *ADARPEF* study, published in 1996, represented regional anaesthesia prior to the advent of ultrasound guidance.[25] The most recent *ADARPEF* study, using the same methodology and comprising 31 132 regional blocks, reported the increased use of peripheral nerve blocks and continuous nerve blocks.[26] The PRAN, now with more than 40 000 blocks in its database, has shown a similar trend, probably indicative of the increased use of laparoscopic surgery, or prompted by fewer complications associated with peripheral nerve blocks noted in earlier surveys.[25,26]

What has not been resolved, despite the many advantages of ultrasound, is whether or not ultrasound-guided blocks are safer than those performed using a nerve stimulator. Meta-analyses of early paediatric studies and those featuring adults were inconclusive.[28,29] Ultrasound-guided nerve blocks are the fashionable expectation in our gadget-orientated society and have virtually become the standard of practice in affluent societies. But less affluent societies should not abandon nerve stimulation and forsake more

important equipment, such as pulse oximetry,[30] for the relatively small gain provided by ultrasound.

New approaches

A special themed issue of *Pediatric Anesthesia* and recent reviews[31-34] have focused on various aspects of regional anaesthesia in infants and children. Written by experienced practitioners, and including manuscripts on neuraxial (epidural, caudal and spinal) and peripheral nerve blocks (upper and lower limb, and truncal), as well as head and neck blocks, all of them are valuable resources. Renewed interest in peripheral nerve blocks recently described in children is the focus of this manuscript.

Maxillary nerve block

Cleft palate surgery is not only painful, but may also compromise the airway, particularly in children with craniofacial syndromes. Opiate analgesia has the potential to further compromise the airway, whereas bilateral maxillary nerve block can provide analgesia without the risk of respiratory depression in these vulnerable patients. The approach to the maxillary nerve differs to that in adults since the facial configuration in infants undergoes changes with growth and development. Thus, bilateral maxillary nerve block is performed using a suprazygomatic approach,[35] and is based on a computer tomography study.[36] Despite the bony nature of the area, an ultrasound approach is also feasible.[37] The block is remarkably easy to perform. Early indications suggest a low complication rate, and it also seems to improve pain relief, to decrease the perioperative consumption of opioids, and to favour early feeding resumption after cleft palate repair in infants.[36]

Transversus abdominis plane blocks

The transversus abdominis plane block (TAP) has recently been described for pain management following abdominal surgery in infants and children.[38-41] The mid-axillary line in-plane approach used in adults for the ultrasound-guided TAP block is not always feasible in small children because access to the space between the thoracic cage and the iliac crest is limited. An anterior-posterior, in-plane approach, with the probe almost vertical to the bed, is more user-friendly in infants and children.[38,39]

The appropriate dosing guidelines and the extent of spread of local anaesthesia have been the subject of debate,[39] and may explain the mixed success achieved with this block when used for upper and lower abdominal surgery. The extent of the spread using 0.2 ml/kg, the recommended paediatric guideline, has been questioned.[38,39] The unpredictability of TAP blocks was demonstrated in a recent study, where the dermatomal spread was assessed in 35 blocks using 0.4 ml/kg.[40] The median level of blockade ranged from T10 to L1 in 75% of the children. Therefore, it has been argued that TAP blocks should be offered for lower abdominal surgery only.[40] In my opinion, TAP blocks are most useful for open appendectomy, colostomy closure, inguinal and other lower abdominal surgery.

While technically challenging in neonates because of their compliant abdominal wall, TAP blocks have been used as an alternative to neuraxial blocks or wound infiltration to provide analgesia for both major and minor neonatal surgery.[41]

Lumbar plexus blocks

Lumbar plexus blocks are considered to be difficult blocks to perform in view of the potential risks involved.[42-47] The femoral, obturator and lateral femoral cutaneous nerves that supply the anterior aspect of the lower limb are more reliably blocked with a lumbar plexus block than a three-in-one block. Several approaches to the lumbar plexus that rely on bony contact with the transverse process of L4 have been described in adults. The transverse processes are not fully developed in children, and using the transverse process as a guide, place the needle too medial, increasing the risk of puncturing a dural cuff on the spinal roots or retrograde epidural spreading to the opposite side.[42]

Ultrasound guidance, while feasible, is limited to younger children because the definition obtained with linear probes from portable ultrasound units is inadequate for accurate placement if the lumbar plexus is deeper than 4-5 cm. Many advocate combining ultrasound with a nerve stimulator. An approach that the author has found to be useful is a modification of Winnie, Ramamurthy, Durani and Radonjic's approach.[43] With the child in a lateral position, an insulated needle that is inserted perpendicular to the skin at the point where a line drawn from the posterior superior iliac spine, parallel to the spinous processes of the vertebrae, intersects the intercristal (Touffier's) line, will advance through the posterior lumbar fascia, paraspinous muscles, anterior lumbar fascia, quadratus lumborum and into the psoas muscle.[44] Passage through these fascial layers may be detected by distinct "pops" when using a short bevelled needle. Quadriceps muscle twitches in the ipsilateral thigh are sought, confirming stimulation of the lumbar plexus. The depth from the skin to the lumbar plexus is approximately the same distance as that of the posterior superior iliac spine to the intercristal line.[44] The depth of the needle is emphasised because of complications associated with wayward needle advancement into the peritoneum or retroperitoneum which may result in a renal haematoma, vascular puncture (retroperitoneal haematoma), or even bowel puncture.

Methods to increase the duration of analgesia

Continuous peripheral nerve blocks

Continuous peripheral nerve catheters have not been readily available for use in children until recently. Nowadays, continuous postoperative pain management or pain

therapy is feasible in older children and adolescents, but improvement is still necessary in infants and small children.[48-58] The main indications are children undergoing procedures or with conditions[51] that are associated with significant or prolonged postoperative pain, and to improve peripheral perfusion after microvascular surgery or in vasospastic disorders involving the limbs. Patient-controlled analgesia is also feasible in selected cases. Continuous infusion has also been used to provide analgesia in order to allow physical therapy in cases involving chronic regional pain syndromes. The blood level of local anaesthetic agents, reached during continuous brachial plexus infusion, is less than that reached during continuous epidural analgesia. Accurate placement can be confirmed with real-time ultrasound imaging or fluoroscopically.

The main indication for the lower extremity block has been the management of femur fractures[50,52] or major trauma that involves the lower limb. Catheters have also been placed in the lumbar plexus[53] or fascia iliaca compartment[54] to provide unilateral analgesia of the hip or thigh. The fixation of catheters for continuous use is considered to be easier on the lower extremity,[58] particularly for lumbar plexus blocks.[44]

Ideally, a commercially available kit should be used as it allows the use of a nerve stimulator to identify the nerve sheath prior to placement of the catheter. Several manufacturers now provide insulated Tuohy® needles of child-friendly length through which an appropriate-sized catheter can be passed. The role of stimulating versus non-stimulating catheters for continuous peripheral nerve blocks is the subject of ongoing research.

The recommended dosage for continuous infusion after an initial bolus dose is 0.1-0.2 ml/kg/hour of either bupivacaine or levobupivacaine (0.125-0.25%) or ropivacaine (0.15-0.2%). Generally, the lower rates are used for upper extremity catheters, and the higher rates for lower extremity nerve or plexus analgesia. The infusion rate may be adjusted, as needed, up to the maximum recommended infusion rate of 0.2 mg/kg/hour for infants younger than six months of age, and 0.4 mg/kg/hour for children older than that.[55] Elastomeric devices or disposable infusion pumps that may be programmed to deliver local anaesthetic based on the child's weight are currently available, and may offer an option for outpatient paediatric pain control in the future.[48] To date, the reported complications have been low, but include catheter-induced infection, particularly in immunocompromised patients, haematoma formation, catheter breakage or knot formation on removal.

Adjuvants

Adjuvants are drugs that increase the efficacy or potency of other drugs, when given concurrently. They are used firstly to prolong the duration of analgesia after a single-shot caudal block, and secondly, to improve the quality of the analgesia, while allowing lower local anaesthetic concentrations to be used, thereby reducing the unwanted side-effects of local anaesthetics, such as motor blockade and local anaesthetic toxicity.

Single-shot caudals with bupivacaine, ropivacaine or levobupivacaine are safe and effective, but only provide analgesia for 4-6 hours.[59] Since continuous infusion of local anaesthetic agents has a relatively narrow margin of safety in young infants and children, a variety of agents have been used as adjuvants to prolong the analgesic efficacy of caudal, neuraxial, and even peripheral nerve blockade.[60-66] In choosing an adjuvant, the anaesthesia provider must balance the benefits against the potential risks, taking into account the age of the child, the impact of the co-morbidities, available facilities, and whether or not the child is to be managed in hospital or at home.

Based on current evidence, it is difficult to reach consensus on the most effective adjuvant. There is even less evidence when combinations are used. Most studies on children have used minor surgery (inguinal hernia repair and circumcision) under caudal block as the clinical research model. The heterogeneity of these studies, both in terms of the type and concentration of local anaesthetic agent, as well as the dose of adjuvant used, are all confounding factors that make meta-analyses difficult.[67,68] The studies also vary according to the nature of surgery, the premedication used, the method of pain assessment and the age range of the children. Two surveys of members of the Association of Paediatric Anaesthetists of Great Britain and Ireland have demonstrated an increase over the past decade in the use of adjuvants to enhance the analgesia provided by a caudal block from 58%[69] to almost 80%.[70]

Although many other agents have been studied, the most effective agents in clinical practice are opiates (morphine and diamorphine), and clonidine and ketamine. Clonidine and ketamine have become increasingly popular, while opiates seem to be on the decline, predominantly for their unwanted side-effects.[69,70] Ketamine, particularly racemic ketamine, despite its popularity in some countries, may suffer a similar fate to that of morphine, in view of concerns relating to neurotoxicity.[68]

Clonidine, an alpha 2 agonist, has sedative, analgesic and antihypertensive properties, and is commercially available as a preservative-free preparation. There is good evidence that the major effect of clonidine is mediated at spinal cord level.[71,72] Clonidine 1-2 µg/kg is effective, and typically doubles the duration of the local anaesthetic agent. Higher doses are associated with increasing sedation, bradycardia, hypotension and a risk of apnoea, particularly in neonates and infants. Clonidine 0.1 µg/kg/hour enhances the analgesia of diluted continuous epidural infusion of 0.1% bupivacaine or ropivacaine.[67,73,74]

A meta-analysis of 20 randomised controlled trials, published between 1994 and 2010, which included 993

patients aged 2-6 years undergoing urogenital or lower limb surgery, showed a longer duration of postoperative analgesia in those receiving clonidine 0.1 µg/kg in addition to a local anaesthetic [mean difference (MD): 3.72 hours; 95% confidence interval (CI): 2.61-4.84, p-value < 0.00001], with a lower risk of rescue analgesia [relative risk (RR): 0.72, 95% CI: 0.57-0.90, p- value 0.003] than local anaesthetic alone.[67]

Clonidine seems to have a large margin of safety based on three cases where 100 times the intended dose of caudal clonidine was administered to children aged 14 months to five years, without any untoward cardiorespiratory effects. All were somnolent for 24 hours and made a full recovery.[75] Several cases of respiratory depression and apnoea have been reported in preterm and term neonates, probably relating to immature respiratory control and central sedation.[76,77] Therefore, clonidine is not recommended for infants, particularly preterm infants younger than three months of age, in view of this risk of apnoea.

Ketamine, a noncompetitive spinal N-methyl-D-aspartate and mild mu receptor agonist, is most effective as an adjuvant for caudal block at doses of 0.25-1 mg/kg.[68,78] The same dose given intravenously has a much shorter duration of action, but ketamine can exceed clonidine if given caudally.[78] Higher doses increase the incidence of unwanted side-effects (sedation, hallucinations, nystagmus, nausea and vomiting), with little further improvement in analgesia.

In a similar quantitative review and meta-analysis of 13 randomised controlled trials published between 1991 and 2008, that included 584 patients aged 2-12 years undergoing urogenital or lower limb surgery, ketamine 0.25-0.5 mg/kg, combined with a single dose of local anaesthetic (ropivacaine or bupivacaine), had a longer duration of analgesia (MD: 5.6 hours, 95% CI: 5.45-5.76, p-value < 0.00001) with a lower relative risk of rescue analgesia (RR: 0.71, 95% CI: 0.44-1.15, p-value 0.16), than local anaesthetic alone, despite the heterogeneity of groups in the different studies.[68]

The preservatives, benzethonium chloride and chlorbutanol, in the commercially available product were implicated in the histopathological changes demonstrated in animal models, but not in humans. This has raised concerns in some quarters. Despite numerous studies showing no ill effects, as a result, ketamine is no longer recommended as an adjuvant in Germany, Switzerland and Austria. Preservative-free racemic ketamine and S(+)-ketamine are available in some countries. S(+)-ketamine has twice the analgesic potency of the racemate, with fewer side-effects.[79]

Although both clonidine and ketamine increase the duration of analgesia, when used in combination, S(+)-ketamine and clonidine can provide satisfactory analgesia for up to 20 hours. To put this into perspective, it is worth considering that other regional techniques, such as a penile, TAP, and ilioinguinal block, may offer longer or comparable duration of analgesic without the concerns just outlined.[80,81]

It is difficult to advocate the use of other drugs that contain potentially harmful preservatives, or any drug that has not undergone proper safety evaluation. Agents such as midazolam,[82,82] neostigmine,[83,84] and to a lesser extent, tramadol and buprenorphine, fall into this category. They all produce a limited increase in analgesia, but are associated with an unacceptably high incidence of nausea and vomiting.

Peripheral nerve block adjuvants

A variety of adjuvants have been used to supplement local anaesthetics in peripheral nerve blocks, with mixed results. A qualitative systematic review of 27 studies in adults, where clonidine was used in peripheral nerve blocks, was proved to be inconclusive.[85]

Until recently, there have been few studies on children. In a retrospective audit of 220 children at one institution aged 2-19 years who received clonidine in combination with bupivacaine or ropivacaine for a variety of blocks (brachial and lumbar plexus, femoral, fascia iliaca or sciatic nerve), it was found that the sensory block was extended by a few hours, but the incidence of motor block was increased, when compared to the 215 children who had received plain bupivacaine or ropivacaine.[86]

Clonidine did not prolong the duration of ilioinguinal blocks with 0.25% bupivacaine in 98 children aged 1-12 years undergoing inguinal hernia surgery.[87,88] Clonidine did not improve the quality of analgesia, but prolonged the duration of analgesia of an axillary block with 0.2% ropivacaine in 30 children aged 1-6 years.[89]

These findings are not surprising since there are no alpha 2-adrenergic receptors in peripheral nerves.[90] Based on animal studies, the mechanism of action is thought to be either vasoconstriction [90] or possibly membrane hyperpolarisation-activated cation currents.[91,92]

Summary

Paediatric regional anaesthesia continues to grow, particularly in the day surgery setting, because of the many outlined advantages.[2] Patient safety should remain the focus when performing regional anaesthesia. The choice of regional technique should be considered within the context of risk versus benefit, based on the age of the child, the nature of the surgery, the available facilities and equipment, and the skill of the practitioner.

In the future, technological advances will improve the image quality of ultrasonograhy. The challenge in the future will be to determine which modality will be the most cost-effective to further broaden the horizons of paediatric regional anesthesia.

Regional anaesthesia cannot move forward without the support of the whole surgical team. Education at all levels is essential, e.g. surgeon and nurse, patient and family, and

anaesthetic colleagues and trainees, particularly when a continuous infusion is used. A successful block sells itself. The future challenge will be to achieve success safely and to further reduce the documented risk.

References

1. Bosenberg A. Benefits of regional anesthesia in children Paediatr Anaesth. 2012;22(1):10-18.
2. Bosenberg AT, Jöhr M, Wolf AR. Pro con debate: the use of regional vs systemic analgesia for neonatal surgery. Paediatr Anaesth. 2011;21(12):1247-1258.
3. Llewellyn N, Moriarty A. The national pediatric epidural audit. Paediatr Anaesth. 2007;17(6):520-533.
4. Morton NS, Errera A. APA national audit of pediatric opioid infusions. Pediatr Anesth. 2010;20(2):119-125.
5. Polaner DM, Drescher J. Pediatric regional anesthesia: what is the current safety record? Pediatr Anesth. 2011;21(7):737-742.
6. Willschke H, Marhofer P, Machata AM, Lönnqvist PA. Current trends paediatric regional anaesthesia. Anaesthesia. 2010;65 Suppl 1:97-104.
7. Gunter JB. Benefits and risks of local anesthetics in infants and children. Pediatr Drugs. 2002;4(10):649-672.
8. Lönnqvist PA. Regional anaesthesia and analgesia in the neonate. Best Pract Res Clin Anaesthesiol. 2010;24(3):309-321.
9. Rochette A, Dadure C, Raux O, et al. A review of pediatric regional anesthesia practice during a 17-year period in a single institution. Pediatr Anesth. 2007;17(9):874-880.
10. Polaner DM, Bosenberg A, Taenzer A, et al. Preliminary data from the Pediatric Regional Anesthesia Network (PRAN); demographics, practice patterns, and complications. New Orleans: American Society Anesthesiologists Annual Meeting; 2009.
11. Polaner DM, Martin LD, PRAN investigators. Quality assurance and improvement: the Pediatric Regional Anesthesia Network. Paediatr Anaesth. 2012;22(1):115-119.
12. Denny NM, Harrop-Griffiths W. Location, location, location! Ultrasound imaging in regional anaesthesia. Br J Anaesth. 2005;94(1):1-3.
13. Bosenberg AT. Regional anaesthesia: children are different. Pediatr Anesth. 1998;8(6):447-450.
14. Bosenberg AT, Raw R, Boezaart AP. Surface mapping of peripheral nerves in children with a nerve stimulator. Paediatr Anaesth. 2002;12(5):398-403.
15. Hadzic A. Peripheral nerve stimulators: cracking the code: one at a time. Reg Anesth Pain Med. 2004;29(3):185-188.
16. Tsui BCH, Hui Yun Ip V. Ultrasound beyond regional anesthesia. Can J Anesth. 2011;58(6):499-503.
17. Regional Anesthesiology and Acute Pain Medicine Fellowship Directors Group. Guidelines for fellowship training in regional anesthesiology and acute pain medicine: Second Edition, 2010. Reg Anesth Pain Med. 2011;36(3):282-288.
18. Sites BD, Chan VW, Neal JM, et al. The American Society of Regional Anesthesia and Pain Medicine and the European Society of Regional Anaesthesia and Pain Therapy joint committee recommendations for education and training in ultrasound-guided regional anesthesia. Reg Anesth Pain Med. 2010;35(2 Suppl):S74-S80.
19. Bröking K, Waurick R. How to teach regional anesthesia. Curr Opin Anaesthesiol. 2006;19(5):526-530.
20. Hargett MJ, Beckman JD, Liguori GA, Neal JM. Education Committee in the Department of Anesthesiology at Hospital for Special Surgery. Guidelines for regional anesthesia fellowship training. Reg Anesth Pain Med. 2005;30(3):218-225.
21. Smith HM, Kopp SL, Jacob AK, et al. Designing and implementing a comprehensive learner-centered regional anesthesia curriculum. Reg Anesth Pain Med. 2009;34(2):88-94.
22. Hocking G, Hebard S, Mitchell CH. A review of the benefits and pitfalls of phantoms in ultrasound-guided regional anesthesia. Reg Anesth Pain Med. 2011;36(2):162-170.
23. Sites BD, Neal JM, Chan V. Ultrasound in regional anesthesia: where should the "focus" be set? Reg Anesth Pain Med. 2009;34(6):531-533.
24. Wynd KP, Smith HM, Jacob AK, et al. Ultrasound machine comparison: an evaluation of ergonomic design, data management, ease of use, and image quality. Reg Anesth Pain Med. 2009;34(4):349-356.
25. Giaufre E, Dalens B, Gombert A. Epidemiology and morbidity of regional anesthesia in children: a one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists. Anesth Analg. 1996;83(5):904-912.
26. Ecoffey C, Lacroix F, Giaufre E, et al. Epidemiology and morbidity of regional anesthesia in children: a follow-up one-year prospective survey of the French-Language Society of Paediatric Anaesthesiologists (ADARPEF). Paediatr Anaesth. 2010;20(12):1061-1069.
27. Polaner DM, Walker BJ, Taenzer A, et al. Pediatric Regional Anesthesia Network: a multi-institutional study of the use and incidence of complications of pediatric regional anesthesia. Anesth Analg. 2012;115(6):1353-1364.
28. Ting PH, Antonakakis JG. Evidence based review of ultrasound imaging for regional anesthesia. Seminars Anesthesia Perioperative Medicine Pain. 2007;26:218-228.
29. Rubin K, Sullivan D, Sadhasivam S. Are peripheral and neuraxial blocks with ultrasound guidance more effective and safe in children? Paediatr Anaesth. 2009;19(2):92-96.
30. Walker IA, Newton M, Bosenberg AT. Improving surgical safety globally: pulse oximetry and the WHO Guidelines for Safe Surgery. Paediatr Anaesth. 2011;21(7):825-828.
31. Lonnqvist PA. Themed issue "Pediatric Regional Anesthesia": starting 2012 with a bang! Paediatr Anaesth. 2012;22(1):1-118.
32. Suresh S, Voronov P. Head and neck blocks in infants, children, and adolescents. Paediatr Anaesth. 2012;22(1):81-87.
33. Tsui BC, Suresh S. Ultrasound imaging for regional anesthesia in infants, children, and adolescents: a review of current literature and its application in the practice of neuraxial blocks. Anesthesiology. 2010;112(3):719-728.
34. Tsui B, Suresh S. Ultrasound imaging for regional anesthesia in infants, children, and adolescents: a review of current literature and its application in the practice of extremity and trunk blocks. Anesthesiology. 2010;112(2):473-492.
35. Captier G, Dadure C, Leboucq N, et al. Anatomic study using three-dimensional computed tomographic scan measurement for truncal maxillary nerve blocks via the suprazygomatic route in infants. J Craniofac Surg. 2009;20(1):224-228.
36. Mesnil M, Dadure C, Captier G, et al. A new approach for peri-operative analgesia of cleft palate repair in infants: the bilateral suprazygomatic maxillary nerve block. Paediatr Anaesth. 2010;20(4):343-349.
37. Sola C, Raux O, Savath L, et al. Ultrasound guidance characteristics and efficiency of suprazygomatic maxillary nerve blocks in infants: a descriptive prospective study. Paediatr Anaesth. 2012;22(9):841-846.
38. Suresh S, Chan VW. Ultrasound guided transversus abdominis plane block in infants, children and adolescents: a simple procedural guidance for their performance. Paediatr Anaesth. 2009;19(4):296-299.
39. Charlton S, Cyna AM, Middleton P, Griffiths JD. Perioperative transversus abdominis plane (TAP) blocks for analgesia after abdominal surgery. [Cochrane review]. In: The Cochrane Library, Issue 12; 2010. Oxford: Update Software.
40. Palmer GM, Luk VH, Smith KR, Prentice EK. Audit of initial use of the ultrasound-guided transversus abdominis plane block in children. Anaesth Intensive Care. 2011;39(2):279-286.
41. Fredrickson MJ, Seal P. Ultrasound-guided transversus abdominis plane block for neonatal abdominal surgery. Anaesth Intensive Care. 2009;37(3):469-472.
42. Dalens B, Tanguy A, Vanneuville G. Lumbar plexus block in children: a comparison of two procedures in 50 patients. Anesth Analg. 1988;67(8):750-758.
43. Winnie A, Ramamurthy S, Durani Z, Radonjic R. Plexus blocks for lower extremity surgery: new answers to old problems. Anesthesiol Rev. 1974;1:11-16.
44. Walker BJ, Flack SH, Bosenberg A. Predicting lumbar plexus depth in children and adolescents. Anesth Analg. 2011;112(3):661-665.
45. Mello S, Saraiva R, Marques R, et al. Posterior lumbar plexus block in children: a new anatomical landmark. Reg Anesth Pain Med. 2007;32(6):522-527.
46. Dadure C, Raux O, Gaudard P, et al. Continuous psoas compartment blocks after major orthopedic surgery in children: a prospective computed tomographic scan and clinical studies. Anesth Analg. 2004;98(3):623-628.
47. Kirchmair L, Enna B, Mitterschiffthaler G, et al. Lumbar plexus in children. A sonographic study and its relevance to pediatric regional anesthesia. Anesthesiology. 2004;101(2):445-450.

48. Dadure C, Raux O, Troncin R, et al. Continuous infraclavicular brachial plexus block for acute pain management in children. Anesth Analg. 2003;97(3):691-693.
49. Lehtipalo S, Koskinen LO, Johansson G, et al. Continuous interscalene brachial plexus block for postoperative analgesia following shoulder surgery. Acta Anaesthesiol Scand. 1999;4393):258-264.
50. Tobias JD. Continuous femoral nerve block to provide analgesia following femur fracture in a paediatric ICU population. Anaesth Intensive Care. 1994;22(5):616-618.
51. Diwan R, Lakshmi V, Shah T, et al. Continuous axillary block for upper limb surgery in a patient with epidermolysis bullosa simplex. Paediatr Anaesth. 2001;11(5):603-606.
52. Johnson CM. Continuous femoral nerve blockade for analgesia in children with femoral fractures. Anaesth Intensive Care. 1994;22(3):281-283.
53. Sciard D, Matuszczak M, Gebhard R, et al. Continuous posterior lumbar plexus block for acute postoperative pain control in young children. Anesthesiology. 2001;95(6):1521-1523.
54. Paut O, Sallabery M, Schreiber-Deturmeny E, et al. Continuous fascia iliaca compartment block in children: a prospective evaluation of plasma bupivacaine concentrations, pain scores, and side effects. Anesth Analg. 2001;92(5):1159-1163.
55. Berde CB. Toxicity of local anesthetics in infants and children. J Pediatr. 1993;122(5 Pt 2):S14-S20.
56. Dadure C, Raux O, Gaudard P, et al. Continuous psoas compartment blocks after major orthopedic surgery in children: a prospective computed tomographic scan and clinical studies. Anesth Analg. 2004;98(3):623-628.
57. Dadure C, Pirat P, Raux O, et al. Perioperative continuous peripheral nerve blocks with disposable infusion pumps in children : a prospective descriptive study. Anesth Analg. 2003;97(3):687-690.
58. Ponde VC, Desai AP, Shah DM, Johari AN. Feasibility and efficacy of placement of continuous sciatic perineural catheters solely under ultrasound guidance in children: a descriptive study. Paediatr Anaesth. 2011;21(4):406-410.
59. Dobereiner EF, Cox RG, Ewen A, Lardner DR. Evidence-based clinical update: Which local anesthetic drug for pediatric caudal block provides optimal efficacy with the fewest side effects? Can J Anaesth. 2010;57(12):1102-1110.
60. Lonnqvist PA, Ivani G, Moriarty T. Use of caudal-epidural opioids in children: still state of the art or the beginning of the end? Paediatr Anaesth. 2002;12(9):747-749.
61. Lonnqvist PA, Morton NM. Postoperative analgesia in infants and children. Br J Anaesth. 2005;95(1):59-68.
62. De Beer DAH, Thomas ML. Caudal additives in children-solutions or problems! Brit J Anesth. 2003;90(4):487-498.
63. Lonnqvist PA. Adjuncts to caudal block in children: quovadis? Br J Anaesth. 2005;95(4):431-433.
64. Mazoit JX. Local anesthetics and their adjuncts. Pediatr Anesth. 2012;22(1):31-38.
65. Krane EJ, Jacobson LE, Lynn AM, et al. Caudal morphine for postoperative analgesia in children: a comparison with caudal bupivacaine and intravenous morphine. Anesth Analg. 1987;66(7):647-653.
66. Disma N, Frawley G, Mameli L, et al. Effect of epidural clonidine on minimum local anesthetic concentration (ED50) of levobupivacaine for caudal block in children. Paediatr Anaesth. 2001;21(2):128-135.
67. Schnabel A, Poepping DM, Pogatzki-Zahn EM, Zahn PK. Efficacy and safety of clonidine as additive for caudal regional anesthesia: a quantitative systematic review of randomized controlled trials. Paediatr Anaesth. 2011;21(12):1219-1230.
68. Schnabel A, Poepping DM, Kranke P, et al. Efficacy and adverse effects of ketamine as an additive for paediatric caudal anaesthesia: a quantitative systematic review of randomized controlled trials. Br J Anaesth. 2011;107(4):601-611.
69. Sanders JC. Paediatric regional anaesthesia, a survey of practice in the United Kingdom. Br J Anaesth. 2002;89(5):707-710.
70. Menzies R, Congreve K, Herodes V, et al. A survey of pediatric caudal extradural anesthesia practice. Paediatr Anaesth. 2009;19(9):829-836.
71. Akin A, Ocalan S, Esmaoglu A, Boyaci A. The effects of caudal or intravenous clonidine on postoperative analgesia produced by caudal levobupivacaine in children. Paediatr Anaesth. 2010;20(4):350-355.
72. Castro MI, Eisenach JC. Pharmacokinetics and dynamics of intravenous, intrathecal, and epidural clonidine in sheep. Anesthesiology. 1989;71(3):418-425.
73. Constant I, Gall O, Gouyet L, et al. Addition of clonidine or fentanyl to local anaesthetics prolongs the duration of surgical analgesia after single shot caudal block in children. Br J Anaesth. 1998;80(3):294-298.
74. Yildiz TS, Korkmaz F, Solak M, Toker K. Clonidine addition prolongs the duration of caudal analgesia. Acta Anaesthesiol Scand. 2006;50(4):501-504.
75. Meyer C, Cambray R. One hundred times the intended dose of caudal clonidine in three pediatric patients. Paediatr Anaesth. 2008;18(9):888-890.
76. Bouchut JC, Dubois R, Godard J. Clonidine in preterm-infant caudal anesthesia may be responsible for postoperative apnea. Reg Anesth Pain Med. 2001;26(1):83-85.
77. Fellmann C, Gerber AC, Weiss M. Apnoea in a former preterm infant after caudal bupivacaine with clonidine for inguinal herniorrhaphy. Paediatr Anaesth. 2002;12(7):637-640.
78. Martindale SJ, Dix P, Stoddart PA. Double-blind randomized controlled trial of caudal versus intravenous S(+)-ketamine for supplementation of caudal analgesia in children. Br J Anaesth. 2004;92(3):344-347.
79. Hager H, Marhofer P, Sitzwohl C, et al. Caudal clonidine prolongs analgesia from caudal S(+)-ketamine in children. Anesth Analg. 2002;94(5):1169-1172.
80. Margetts L, Carr A, McFadyen G, Lambert A. A comparison of caudal bupivacaine and ketamine with penile block for paediatric circumcision. Eur J Anaesthesiol. 2008;25(12):1009-1013.
81. Gauntlett I. A comparison between local anaesthetic dorsal nerve block and caudal bupivacaine with ketamine for paediatric circumcision. Paediatr Anaesth. 2003;13(1):38-42.
82. Kumar P. Caudal additives in pediatrics: a comparison among midazolam, ketamine, and neostigmine coadministered with bupivacaine. Anesth Analg. 2005;101(1):69-73.
83. Batra YK, Arya VK, Mahajan R, Chari P. Dose response study of caudal neostigmine for postoperative analgesia in paediatric patients undergoing genitourinary surgery. Paediatr Anaesth. 2003;13(6):515-521.
84. Almenrader N, Passariello M, D'Amico G, et al. Caudal additives for postoperative pain management in children: S(+)-ketamine and neostigmine. Paediatr Anaesth. 2005;15(2):143-147.
85. McCartney CJL, Duggan E, Apatu E. Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. Reg Anesth Pain Med. 2007;32(4):330-338.
86. Cucchiaro G, Ganesh A. The effects of clonidine on postoperative analgesia after peripheral nerve blockade in children. Anesth Analg. 2007;104(3):532-537.
87. Kaabachi O, Zerelli Z, Methamem M, et al. Clonidine administered as adjuvant for bupivacaine in ilioinguinal-iliohypogastric nerve block does not prolong postoperative analgesia. Paediatr Anaesth. 2005;15(7):586-590.
88. Ivani G, Conio A, De Negri P, et al. Spinal versus peripheral effects of adjunct clonidine: comparison of the analgesic effect of a ropivacaine-clonidine mixture when administered as a caudal or ilioinguinal-iliohypogastric nerve blockade for inguinal surgery in children. Paediatr Anaesth. 2002;12(8):680-684.
89. Trifa M, Ben Khalifa S, Jendoubi A, et al. Clonidine does not improve quality of ropivacaine axillary brachial plexus block in children. Paediatr Anaesth. 2012;22(5):425-429.
90. Lönnqvist PA. Alpha-2 adrenoceptor agonists as adjuncts to peripheral nerve blocks in children: is there a mechanism of action and should we use them? Paediatr Anaesth. 2012;22(5):421-424 .
91. Gaumann DM, Brunet PC, Jirounek P. Hyperpolarizing after potentials in C fiber and local anesthetic effects of clonidine and lidocaine. Pharmacology. 1994;48(1):21-29.
92. Kroin JS, Buvanendran A, Beck DR, et al. Clonidine prolongation of lidocaine analgesia after sciatic nerve block in rats is mediated via the hyperpolarization-activated cation current, not by alpha-adrenoreceptor. Anesthesiology. 2004;101(2):488-494.