REVIEW

The European society of regional anesthesia and pain therapy and the American society of regional anesthesia and pain medicine joint committee practice advisory on controversial topics in pediatric regional anesthesia I and II: what do they tell us?

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Purpose of review
To summarize the two recent sets of European and American Societies of Regional Anesthesia (ESRA-ASRA) Practice Advisory Guidelines for the performance of pediatric regional anesthesia (PRA).

Recent findings
Owing to the still ongoing debate regarding crucial issues concerning the effective and safe conduct of PRA and because of the lack of any generally accepted guidelines regarding PRA the (ESRA-ASRA) have addressed these in two topical publications.

Summary
Following an extensive literature search and an evidence-based approach the ESRA-ASRA task force have now provided a practice advisory on the following hot topics in PRA: the safety and appropriateness of placing block during general anesthesia or deep sedation, the use of test dosing, whether to use air or saline when performing loss-of-resistance, the risk of masking an acute compartment syndrome by use of PRA, dosing of local anesthetics for neuroaxial nerve blocks as well as peripheral nerve blocks, and finally the use of various drugs as adjuncts to local anesthetics.

Keywords
guidelines, local anesthetics, pediatric, regional anesthesia

INTRODUCTION

In the early 20th century, pediatric regional anesthesia (PRA) was practiced at certain centers and two of the patients in Bier's first publication on spinal anesthesia were in fact children. With the introduction of safer and more efficacious anesthesia techniques PRA was less frequently practiced. During the 1980s PRA again became popular, including the use of epidural anesthesia in children [1].

Ever since the 1980s, several issues have remained points of discussion regarding the appropriate practice of PRA as no consensus or guidelines have been produced. In response to this unsatisfactory situation, the European and American Societies of Regional Anesthesia (ESRA-ASRA) in 2012 decided to make a

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Curr Opin Anesthesiol 2017, 30:000–000
DOI:10.1097/ACO.0000000000000508

KEY POINTS

- The performance of PRA under general anesthesia/deep sedation is associated with acceptable safety and should be viewed as the standard of care.
- Because of the difficulty interpreting a negative test dose, the use of test dosing should remain discretionary.
- If either technique is used appropriately, either air-LOR and saline-LOR techniques may be safely used in infants and children.
- There is no current evidence that the use of regional anesthetics increases the risk for ACS or delays its diagnosis in children.
- Ropivacaine 0.2% (2 mg/ml) or levobupivacaine/bupivacaine 0.25% (2.5 mg/ml) is recommended for the performance of caudal blocks in children and should not exceed 2 mg/kg ropivacaine or 2.5 mg/kg bupivacaine or levobupivacaine.
- When using continuous infusions of local anesthetics for peripheral nerve and fascial plane blocks the following dosages should be adhered to: Racemic bupivacaine, levobupivacaine 0.125% or ropivacaine 0.2% with an infusion rate of 0.1–0.3 mg/kg/h.
- There is a solid evidence base for the use of clonidine as an adjunct to local anesthetics for both neuroaxial and peripheral nerve blocks in children.

combined effort to clarify the situation by producing common practice advisory guidelines regarding different issues that have been the focus for debate.

ESRA-ASRA appointed an equal number of experts in the field of PRA to be part of the creation of the advisory guidelines. To promote an evidence-based approach, thorough literature searches were performed with regards to each individual topic. Each topic was subsequently handled by two reviewers and the recommendations were subsequently reviewed by all the other task force delegates. The evidence-based grading system is shown in Table 1.

In total, seven individual topics were covered in two separate publications [2▪▪,3▪▪]. It was initially intended to also include the topic of local anesthetic toxicity in the second part of the advisory guidelines but the final decision was not to do so. However, this summary of the advisory guidelines also include a brief section on this topic.

Performing nerve blocks in anesthetized or deeply sedated children

As safety is of the utmost importance in PRA several large scale (10 000–50 000 patients) prospective observational studies have now been carried out and reported in the literature [4–7].

Of special interest in this context is data reported from the PRA Network (PRAN) that specifically compared complications following block placement awake or lightly sedated vs. anesthetized or deeply sedated [8]. No difference in local anesthetic systemic toxicity (LAST) could be identified but placing blocks in awake or lightly sedated children was associated with a higher incidence of postoperative neurologic symptoms.

Conclusions/recommendations

(1) The performance of PRA under general anesthesia/deep sedation is associated with acceptable safety and should be viewed as the standard of care (Evidence B2 and Evidence B3).
(2) The overall risk for complications is 0.66% (95% confidence interval, 0.6–0.7%), whereas the risk of paralysis is estimated at 0 (95% confidence interval, 0–0.004%; Evidence B2 and Evidence B3).
(3) Despite the reassuring safety of PRA performed under general anesthesia/deep sedation, serious complications may still occur. In the event of an unexpected clinical outcome, especially unanticipated motor blockade during continuous postoperative regional block after the use of PRA, a high index of suspicion for neurological injury is warranted and appropriate diagnostic and therapeutic measures must be performed without delay (Evidence B4).

The use of test dosing

To detect accidental intravascular injection of an local anesthetics solution in children, epinephrine can be added to the local anesthetics solution. However, a small child's increased resting heart rate, combined with the fact that most regional blocks are performed under general anesthesia/deep sedation, means that the utility and accuracy of test dosing remain a matter of controversy among pediatric anesthesiologists. One of the main problems is interpreting the hemodynamic response induced by an intravenous (i.v.) injection of local anesthetics mixed with a small dose of epinephrine [9]. The following factors have been demonstrated or theorized to alter the reliability of a test dose: the general anesthetic agent used and its dose at the time of injection of the test dose; a higher basal heart rate in infants and small children; a possible age-dependent variation of the reactivity of the cardiovascular system to epinephrine; the premedication received; the local anesthetics used; and the general anesthesia technique used [10].

Table 1. Evidence-based classification system

Evidence class	Study design
A1	Sufficient number of RCT to perform a meta-analysis
A2	Several RCTs but not sufficient to perform a meta-analysis
A3	Single RCT
B1	Observational comparisons between clinical investigations for a specific outcome
B2	Observational studies with associative statistics
B3	Noncomparative observational studies with descriptive statistics
B4	Case reports

RCT, randomized controlled trial.
Adapted with permission [2▪▪].

Conclusions/recommendations

(1) Because of the difficulty interpreting a negative test dose, the use of test dosing should remain discretionary. In clinical practice, if a test dose is used, there may be false-negative results, especially when the test dose is only partially administered i.v. or when the general anesthetic agents can blunt the hemodynamic effects of epinephrine. A negative result after the injection of a test dose, therefore, is reassuring but does not rule out vascular placement of needle or catheter. Any injection of an local anesthetics solution should be performed slowly, in small aliquots (0.1–0.2 ml/kg) and with intermittent aspiration and observation of the ECG tracing.
(2) In all experimental studies using the deliberate i.v. injection of an local anesthetics solution containing epinephrine to model accidental i.v. injection, no false-positive results were observed: any modification of the T wave or of the heart rate within 30–90 s after the injection of a test dose should thus be interpreted as an accidental i.v. injection until disproven (Evidence B3).
(3) Imaging modalities (ultrasound, fluoroscopy) may help to avoid or visualize accidental intravascular needle placement in peripheral blocks, but data are lacking in PRA to determine the value of these techniques.

Air or saline for loss-of-resistance

Flandin-Bléty reported four unfortunate cases, where loss-of-resistance (LOR) with air had been used, which resulted in devastating complication (e.g., permanent paraplegia) [11]. Despite other possible explanations for the permanent injuries (e.g., multiple attempts by inexperienced operators), air was still believed to be an important culprit in this context. Furthermore, additional case reports linked the use of air for LOR to the occurrence of air embolism [12–14].

The above led to an editorial by the opinion leaders of the day that only recommend the use of saline for LOR when performing epidural blockade in children.

The recommendation has never been fully accepted internationally and air has remained the preferred medium for LOR in many countries and it has repeatedly been argued that it is not the medium itself that is the problem but more so the volume that is injected during LOR. This should always be kept to a minimum regardless whether air or saline is used.

No proper evidence base is currently available in the published literature to state that either medium is better or safer than the other.

However, an interesting study by Roelants *et al.* [15] have described the use of a hybrid of air and saline that might provide a useful compromise.

Conclusions/recommendations

(1) The use of either air-LOR and saline-LOR techniques are supported by different international experts, and the literature supporting one technique over the other is sparse; as long as either technique is used appropriately, each may be safely used in infants and children. The combination of air and saline may represent a better alternative that will minimize the risk of injecting air and reduce the volume of saline injected. This method is also associated with a low risk for unintentional dural puncture (expert opinion).
(2) There are insufficient data in children to determine if using LOR to air or saline to detect needle entry into the epidural space will result in clinically significant differences regarding safety, accuracy, and subsequent efficacy of the injected local anesthetics (Evidence B3 and Evidence B4). Thus, both the aforementioned alternatives are acceptable if care is taken to keep the injected volume at a minimum.
(3) In neonates and infants, the volume of air contained in the syringe should be limited to less than 1 ml and air injections should not be repeated if multiple attempts are made to enter the epidural space (expert opinion).
(4) Although the committee recognizes that an air embolism with hemodynamic consequences is rare when LOR air is used, enough evidence is lacking regarding the brain safety even for small

amounts of air in the presence of a right-to-left cardiac shunt.

Acute compartment syndrome

The generally accepted diagnostic pressure limit for defining acute compartment syndrome (ACS) is an intracompartmental tissue pressure of more than 30 mmHg, which require immediate intervention (decompression).

In children, the diagnosis is often more difficult (e.g., preverbal children) and the main warning sign is excruciating pain that is not directly related to the trauma itself. The pain is usually resistant to opioid administration.

Regional anesthesia (peripheral single injection or continuous blockade or epidural infusions) has often by surgeons been considered responsible for delaying diagnosis by masking the ischemic pain. However, ischemic and acute nociceptive pain are transmitted by different nerve fibers and if using dilute local anesthetics solutions nociceptive pain is blocked, whereas the sensation and transmission of ischemic pain is preserved. Thus, if significant breakthrough pain occurs in a patient with a previously working continuous regional block, this is almost pathognomonic for ACS.

A delay in the diagnosis of ACS is most usually caused by not properly identifying patients that are at risk of developing ACS and to insufficient postoperative monitoring of these patients.

A thorough literature search could not find any evidence that PRA increases the risk of delaying the diagnosis of ACS [16–18]. Thus, the panel suggested the following best practice guidelines.

Conclusions/recommendations

(1) There is no current evidence that the use of regional anesthetics increases the risk for ACS or delays its diagnosis in children.
(2) A comprehensive preoperative discussion with the patient's family and the surgical team should be performed to inform them of this rare but serious complication.
(3) As with many controversies linked to PRA, it is almost impossible to give unequivocal statements or recommendations. We suggest the following 'best practice rules' to reduce or avoid the risk of compartment syndrome in children undergoing surgery with perioperative PRA:
   (a) Single shot for both peripheral and neuraxial blocks: use 0.1–0.25% bupivacaine, levobupivacaine, or ropivacaine concentrations because they are less likely to mask ischemic pain and/or produce muscle weakness than more concentrated solutions (Evidence B4);
   (b) For continuous infusions, bupivacaine, levobupivacaine, or ropivacaine concentrations should be limited up to 0.1%;
   (c) In cases of patients having tibial compartment surgery or other high-risk surgeries for compartment syndrome, restricting both volume and concentration in sciatic catheters is advisable;
   (d) The use of local anesthetics additives should be with caution because they can increase the duration and/or density of the block;
   (e) High-risk patients should have appropriate follow-up by acute pain services to allow early detection of potential signs and symptoms;
   (f) If ACS is suspected, compartment pressure measurements should be urgently assessed.

Dosing of local anesthetics for central nerve blocks

Spinal anesthesia

Hyperbaric or isobaric bupivacaine, and more recently isobaric levobupivacaine or ropivacaine can be used. In older children, there are few indications for spinal block in view of the short duration of analgesia; indeed, duration of spinal block is shorter in infants than in adults, probably because of the larger volume of cerebralspinal fluid [19].

Conclusion/recommendation

(1) The performance of spinal anesthesia with tetracaine, bupivacaine, or levobupivacaine can be performed with a dose of 1 mg/kg for newborns and infants and a dose of 0.5 mg/kg in older children (>1 year of age). The performance of spinal anesthesia with ropivacaine can be performed in children with a dose of 0.5 mg/kg.

Caudal block: single injection

Recent PRAN data suggest that approximately 25% of patients undergoing a caudal block received a local anesthetic dose with the potential to cause local anesthetic toxicity [20]. The volume injected should be modified to achieve a dermatomal level according to Armitage, that is, 0.5 ml/kg to achieve the sacral dermatomes, 1 ml/kg to achieve the lumbar dermatomes, and 1.25 ml/kg to reach lower thoracic dermatomes [21].

Conclusion/recommendation

Ropivacaine 0.2% (2 mg/ml) or levobupivacaine/bupivacaine 0.25% (2.5 mg /ml) is recommended for the performance of caudal blocks in children and should not exceed 2 mg/kg ropivacaine or 2.5 mg/kg bupivacaine or levobupivacaine.

Lumbar or thoracic epidural

Similar to caudal anesthesia, the use of ropivacaine 0.2% or levobupivacaine/bupivacaine 0.25% is common for lumbar (2/3) or thoracic (1/3) epidural in children. A dose of 0.5 ml/kg is usually used for lumbar epidural initial loading (0,3 ml/kg thoracic epidural initial loading), and 0.25 ml/kg for subsequent 'top-up' to obtain intraoperative analgesia [22].

Conclusion/recommendation

(1) The use of local anesthetics for lumbar or thoracic epidural in children should not exceed a dosage of 1.7 mg/kg of ropivacaine, bupivacaine, or levobupicaine.

Continuous infusion epidural anesthesia

Epidural infusions of ropivacaine provided satisfactory pain relief in neonates and infants less than 1 year. As plasma concentrations of unbound ropivacaine are not influenced by the duration of the infusion, ropivacaine can be safely used for postoperative epidural infusion for 48–72 h [23]. Levels of unbound ropivacaine were higher in the neonates than in the infants, but well below threshold concentrations for central nervous system toxicity in adults, that is, 0.35 mg/l or less. In the first weeks of life, ropivacaine infusion should be used with more caution. Because of concerns about toxicity because of accumulation of amide local anesthetics in infants and young children, chloroprocaine could be an alternative [24].

Conclusion/recommendation

(1) The performance of continuous epidural anesthesia with bupivacaine/levobupivacaine, ropivacaine, chloroprocaine can be performed with a dose of 0.2 mg/kg/h for children less than 3-month old, 0.3 mg/kg/h for children between 3 months and 1-year old, and 0.4 mg/kg/h for children with more than 1 years of age.

Dosing of local anesthetics for peripheral nerve blocks

Since the introduction of ultrasound-guided regional anesthesia, the use of peripheral nerve blocking techniques has increased dramatically [6,7,25]. However, pharmacokinetic–pharmacodynamic data for peripheral nerve blockade are scarce. Furthermore, different peripheral blocks (e.g., upper/lower extremity blocks and fascial plane blocks) obviously require different volumes and concentrations of the local anesthetic.

In summary, it has been difficult to find an evidence-based overview on local anesthetic dosage and concentrations, both for a single shot and continuous infusion peripheral nerve blocks. Thus, the ESRA-ASRA recommendations, therefore, describe the suggested doses for the different nerve blocks when using ultrasound guidance.

Conclusions/recommendations

Upper and lower extremity blocks (e.g., axillary, infra and supraclavicular, interscalene, sciatic, femoral):

(1) Racemic bupivacaine, levobupivacaine, or ropivacaine: 0.5–1.5 mg/kg.

Fascial plane blocks (e.g., transversus abdominis plane, rectus sheath, ilioinguinal–iliohypogastric):

(1) Racemic bupivacaine, levobupivacaine, or ropivacaine: 0.25–0.75 mg/kg.

Continuous infusion of local anesthetics for peripheral nerve and fascial plane blocks:

(1) Racemic bupivacaine, levobupivacaine 0.125%, or ropivacaine 0.2% ropivacaine: infusion rate 0.1–0.3 mg/kg/h.

Use of adjunct drugs to local anesthetics

Rationale for using adjuvants: Most pediatric surgical interventions do not merit the use of more complicated and resource demanding options for postoperative analgesia. Thus, a popular alternative to achieve prolongation of a single-injection nerve block is to use adjuvant drugs that are mixed with the local anesthetics and thereby increase the duration of the nerve block [26,27,28▪].

Fundamental requirements of adjuvant drugs

Not only does there need to be published evidence for an enhanced effect compared to control (plain local anesthetics), a candidate adjuvant has to fulfill some further important requirements (Table 2).

Table 2. Additional beneficial effects of adjuncts

Preferably meta-analysis data should verify the beneficial effect of the adjuvant to recommend routine use outside clinical trials
There should be sufficient insight into the mechanism of action of the adjuvant
The side-effect profile should be tolerable in comparison with the use of plain local anesthetics
The adjuvant must be available as a preservative-free preparation
Overall safety issues must be acceptable

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Toxicity aspects

The more frequently used adjuncts used in PRA have undergone appropriate investigation regarding whether spinal administrations may cause apoptosis of spinal cord neurons in young individuals [29–32]. Local anesthetics (levobupivacaine), preservative-free morphine and clonidine do not appear to be harmful [29,31,32] but ketamine has been found to cause increased apoptosis in this setting [30]. Against this background it has strongly been suggested that new adjunct alternatives should undergo similar testing before being applied in the clinical setting, especially in neonates and small infants [33].

Dexmedetomidine has recently been shown to have positive effects as an adjuvant both for caudal and peripheral nerve blocks in children [34,35]. This drug does also seem to be associated with acceptable safety features [36] and may, thus, be a new interesting alternative in this setting.

CAUDAL AND EPIDURAL BLOCKS

The issues regarding neuroaxial blocks and the use of adjuvant drugs have been highlighted in a recent review [28▪].

Clonidine and dexmedetomidine

Meta-analysis data clearly support a beneficial effect of clonidine as an adjuvant in the caudal block setting [37–39] and dose–response data also support a beneficial effect in the context of continuous epidural infusion [40]. A recent meta-analysis [34] demonstrated that dexmedetomidine also prolongs postoperative pain relief when used as a caudal block adjunct. The effect size of dexmedetomidine appears to be similar to clonidine despite the considerable difference in elimination half-life between these two α2-adrenoceptor agonists [41].

Racemic ketamine and S-ketamine

Meta-analysis data show that ketamine does produce a useful adjuvant effect in the setting of caudal blocks when codelivered with local anesthetics [42,39] and ketamine appears as more effective to prolong postoperative analgesia when compared to clonidine [43]. S-ketamine can also be used [44] and does fortunately only exist as a preservative-free solution.

Preservative-free morphine

Dose-response data are clearly defined, demonstrating that increasing the dose to more than 50 μg/kg will not enhance the effect but only increases the risk for respiratory depression [45].

PERIPHERAL NERVE BLOCKS

α2-adrenoceptor agonists

In the pediatric setting, a large single-center study showed that adjuvant use of clonidine is associated with a prolongation of peripheral block duration in the order of 20–50% [46]. A recent meta-analysis with full access to all raw data of the included randomized controlled trials showed a definite advantage in favor of the use of adjuvant α2-adrenoceptors [47▪▪], a beneficial effect that remained even after the exclusion of the one randomized controlled trials that investigated the use of dexmedetomidine [35].

Conclusions/recommendations

(1) Neuroaxial blocks
   (a) Caudal blocks: meta-analysis data show that adjuvant use of clonidine is associated with improved postoperative analgesia compared with plain local anesthetics. Preservative-free ketamine is also effective in this setting but animal toxicity data suggest that ketamine should be avoided in newborns and infants because of a potential risk of increased neuronal apoptosis within the spinal cord. (Evidence A1).
   (b) Epidural blocks: adjuvant use of preservative-free morphine and clonidine improve the quality of postoperative analgesia (Evidence A3).
   (c) Intrathecal blocks: adjuvant use of preservative-free morphine, synthetic opioids, and clonidine improve the quality and duration of intrathecal blocks (Evidence A3).

(2) Peripheral nerve blocks
   (a) Meta-analysis data show that adjuvant use of preservative-free clonidine is associated with improved postoperative analgesia compare with plain local anesthetics (Evidence A3).

(b) No other adjuvants have been shown to improve postoperative analgesia in the context of peripheral nerve blocks in children.

Local anesthetic systemic toxicity in children

The reported incidence of local anestheticsST in infants and children is remarkably low [4,6,7]. Systemic toxicity requiring intervention is mostly confined to isolated case reports.

An unpublished audit of the first 100 000 blocks in the PRAN database revealed only six reports of cardiac arrest or seizures after bolus administration. A further 12 cases had minor signs of toxicity that were resolved by stopping the infusion (personal communication, Ben Walker, 20 April 2017). Caution should, therefore, be taken when a bolus dose is administered especially on top of a background infusion.

Detection of LAST in children, particularly in the more susceptible infants and neonates, is difficult. Under anesthesia LAST manifests with ECG changes (ST segment changes, ventricular ectopy, ventricular tachycardia, or ventricular fibrillation) and or signs of cardiovascular collapse. Convulsions are difficult to detect under anesthesia but are more obvious during postoperative continuous infusions of local anesthetic agents.

Prevention. The choice of local anesthetic agent is important. Ropivacaine and levobupivacaine are preferable to bupivacaine in view of their lower toxic profile. Regardless of the local anesthetic agent used strict adherence to dosing guidelines and avoiding conditions that predispose to toxicity (e.g., hypoxemia, hypercarbia, and acidosis) is important. Aspiration prior to injection and slow incremental injections (0.1–0.2 ml/kg) and the use of ultrasound are key to reducing the risk of LAST.

MANAGEMENT OF LOCAL ANESTHETIC SYSTEMIC TOXICITY

In the event of cardiovascular collapse or convulsions as a result of LAST, immediate basic life support should be instituted. The following management algorithm should be followed [48].

(1) Stop administration of local anesthetic and call for help;
(2) Immediate hyperventilation with 100% oxygen;
(3) Suppression of seizures if present (midazolam, thiopentone, propofol);
(4) External cardiac massage and;
(5) Epinephrine 1 μg/kg;
(6) Administration of 20% intralipid 1.5 ml/kg i.v. over 1 min. Follow immediately with an infusion at a rate of 0.25 ml/kg/min. Lipid emulsion in propofol should not be used in lieu of intralipid.
   (a) Continue chest compressions (lipid must circulate);
   (b) Repeat bolus every 3–5 min up to 3 ml/kg total dose until circulation is restored;
   (c) Continue infusion until hemodynamic stability is restored;
   (d) Increase the rate to 0.5 ml/kg/min if blood pressure declines;
   (e) A maximum total dose of 10 ml/kg in first 30 min is recommended;
(7) If no response consider extracorporeal membrane oxygenation if available;

To date there have been in the order of 10 case reports of intralipid use for LAST in children of which nine were successful.

CONCLUSION

Evidence-based guidelines regarding controversial issues in the context of PRA has now been made available through the collaborative work between ESRA and ASRA. Practitioners are advised to adhere to these guidelines.

Acknowledgements

We would like to thank task force members Elliott Krane, Francis Veykemanns, David Polander for their contributions to the first ESRA-ASRA guideline publication and Gildasio da Oliveria for his contribution to second ESRA-ASRA guideline publication.

Financial support and sponsorship

The work was sponsored by the European Society of Regional Anaesthesia and the American Society of Regional Anesthesia.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

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