SPECIAL ARTICLE

The European Society of Regional Anaesthesia and Pain Therapy/American Society of Regional Anesthesia and Pain Medicine Recommendations on Local Anesthetics and Adjuvants Dosage in Pediatric Regional Anesthesia

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Background and Objectives: Dosage of local anesthetics (LAs) used for regional anesthesia in children is not well determined. In order to evaluate and come to a consensus regarding some of these controversial topics, The European Society of Regional Anaesthesia and Pain Therapy (ESRA) and the American Society of Regional Anesthesia and Pain Medicine (ASRA) developed a Joint Committee Practice Advisory on Local Anesthetics and Adjuvants Dosage in Pediatric Regional Anesthesia.

Methods: Representatives from both ASRA and ESRA composed the joint committee practice advisory. Evidence-based recommendations were based on a systematic search of the literature. In cases where no literature was available, expert opinion was elicited.

Results: Spinal anesthesia with bupivacaine can be performed with a dose of 1 mg/kg for newborn and/or infant and a dose of 0.5 mg/kg in older children (>1 year of age). Tetracaine 0.5% is recommended for spinal anesthesia (dose, 0.07–0.13 mL/kg). Ultrasound-guided upper-extremity peripheral nerve blocks (eg, axillary, infraclavicular, interscalene, supraclavicular) in children can be performed successfully and safely using a recommended LA dose of bupivacaine or ropivacaine of 0.5 to 1.5 mg/kg. Dexmedetomidine can be used as an adjunct to prolong the duration of peripheral nerve blocks in children.

Conclusions: High-level evidence is not yet available to guide dosage of LA used in regional blocks in children. The ASRA/ESRA recommendations intend to provide guidance in order to reduce the large variability of LA dosage currently observed in clinical practice.

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The worldwide increase in pediatric regional anesthesia (PRA) has prompted the European Society of Regional Anaesthesia and Pain Therapy (ESRA) and the American Society of Regional Anesthesia and Pain Medicine (ASRA) to publish "The European Society of Regional Anaesthesia and Pain Therapy and the American Society of Regional Anesthesia and Pain Medicine Joint Committee Practice Advisory on Controversial Topics in Pediatric Regional Anesthesia."[1] Practice advisories are helpful when evidence-based clinical practice is either not available or inconclusive.[2] Furthermore, practice advisories may highlight the need for additional research that can advance the field.[3,4]

To date, there are no evidence-based recommendations on dose and concentration of local anesthetics (LAs) or adjuvants in children undergoing regional anesthesia. A single editorial published by Berde[5] prior to the introduction of ropivacaine, levobupivacaine, or adjuvants (eg, clonidine, ketamine) is often cited as a reference for dosing guidelines. In addition, many LA dosing studies that have been performed in children often generated inconclusive results.[6–10] As a result of this large knowledge gap, ESRA and ASRA decided to convene a committee to look at an evidence-based approach to dosing guidelines in children.

To the best of our knowledge, no previous practice advisories specifically addressed LA dosage and the use of adjuvants in PRA. ASRA and ESRA expect that the results of this article will be useful not only to pediatric anesthesiologists but also for anesthesiologists who care for children less frequently.

METHODS

We followed the same methodology of our groups' recently published practice advisory on controversial topics in PRA.[1] Representatives from both ASRA and ESRA composed the joint committee practice advisory on LA dosage and adjuvants in PRA. Committee members met in work groups, and decisions on specific topics to be addressed were made through consensus. The committee used similar methodology on the generation of practice advisories previously described by the American and European anesthesiology societies.[11,12] In brief, an evaluation of availability and strength of the evidence was systematically performed. Scientific evidence was obtained by performing a systematic search of literature. All committee members participated in the expert opinion decisions because all involved have had extensive experience (>15 years) on the topic. No clinicians outside the committee were consulted.

Published reports evaluating the LA dosage and adjuvants for regional anesthesia in pediatric patients were searched using the National Library of Medicine's PubMed database, the Cochrane Database of Systematic Reviews, and Google Scholar inclusive up to August 1, 2016. Free text and MeSH terms "block," "regional,"

TABLE 1. Classification of Scientific Evidence

Evidence Class	Study Design
Category A1	Sufficient number of randomized controlled trials to conduct a meta-analysis
Category A2	Several randomized controlled trials but not sufficient to conduct meta-analysis
Category A3	Single randomized controlled trial
Category B1	Observational comparisons between clinical interventions for a specific outcome
Category B2	Observational studies with associative statistics
Category B3	Noncomparative studies with descriptive statistics
Category B4	Case reports

"children," "surgery," "anesthesia," "local," "bupivacaine," "ropivacaine," "adjuvants," "clonidine," "dexmedetomidine," and "pediatric" were used individually and in various combinations. No language restriction was applied. No date limit was used. The search was limited to articles in subjects younger than 18 years. We reviewed the reference lists from identified studies to identify additional studies not found during our primary search. No search was performed for unpublished studies. The scientific evidence was classified according to the quality of research design as presented in Table 1, similar to what has been previously described in other practice advisories.[1]

When the literature search revealed a lack of published studies or when the only evidence was generated from studies with insufficient quality due to methodological constraints, it was deemed as "insufficient literature," and expert opinion from the ASRA/ESRA joint committee was considered.

RESULTS

General Comments on the Use of LAs in Children

Local anesthetics are metabolized by cytochrome P450 (CYP).[13,14] The main CYP isoforms involved are CYP3A4 for lidocaine and bupivacaine and CYP1A2 for ropivacaine. CYP3A4 is not mature at birth but is partly replaced by CYP3A7. At 1 month of age, the intrinsic clearance of bupivacaine is only one-third of that in adults and two-thirds at 6 months. CYP1A2 is not fully mature before the age of 3 years. Indeed, the clearance of ropivacaine does not reach its maximum before the age of 8 years. Finally, the S- and R-enantiomers of LA kinetics are very similar, and the slight differences that have been described do not have any clinical consequences.

Volumes of distribution of LAs in neonates and infants are larger compared with adults, thus decreasing the risk of high serum drug concentrations from occurring after a single injection, but not following several injections.[15] The larger volume of distribution of LAs in children reduces peak plasma concentrations after a single bolus dose. However, the risk of drug accumulation after a continuous infusion or several injections is increased.[16] The volume of distribution of ropivacaine is smaller than that of bupivacaine in adults and probably in children.

Alpha-1 acid glycoprotein is the major protein that binds LAs. Alpha-1 acid glycoprotein concentration is very low at birth and progressively increases during the first year of life. This is why neonates and young infants have a much higher free fraction of LAs than adults. Alpha-1 acid glycoprotein is an acute phase protein, and its concentration increases rapidly in inflammatory states.

Elevated cardiac output in children tends to accelerate the vascular absorption of drugs from tissue, producing higher initial plasma concentrations and decreased duration of action, and has a potential increased-potency LA systemic toxicity.[17,18] The dosage of LAs in children younger than 2 years should be reduced in view of the higher baseline heart rate, which increases vulnerability to cardiac toxicity of LAs. In children younger than 1 year, the risk of systemic toxicity is further enhanced by higher free plasma concentrations of LAs associated with consistently low serum proteins. This risk is even greater before the age of 6 months when the liver is immature and especially when continuous infusions or repeated bolus doses are used.

Duration of spinal block is shorter in infants than in adults, probably due to the larger volume of cerebrospinal fluid.[19] Indeed, a relationship between duration of motor blockade and age has been reported. In addition, there is a proportionally greater blood flow to the spinal cord with a more rapid uptake of drugs from the subarachnoid space. These phenomena are most pronounced in preterm infants compared with full-term infants.

The long-acting agents ropivacaine and levobupivacaine are less cardiotoxic than and have similar intensity and duration of analgesia to those of racemic bupivacaine.[20–22] Ropivacaine causes less intense motor blockade than racemic bupivacaine when performing neuraxial anesthesia. The levobupivacaine when used for the same indications causes less intense motor blockade than racemic bupivacaine. The intensity of the block is equivalent to or stronger than that of ropivacaine. Table 2 describes onset, duration of action, and potency of various LAs in children.

Local Anesthetics and Neuraxial Blocks

Spinal Anesthesia

Tetracaine 0.5% in 5% dextrose is the most common LA used for spinal anesthesia over the past few decades: 0.13 mL/kg (ie, 1 mg/kg) in infants weighing less than 4 kg and 0.07 mL/kg (ie, 0.5 mg/kg) in infants weighing more than 4 kg.[23,24] Hyperbaric or isobaric bupivacaine, isobaric levobupivacaine, or ropivacaine can also be used.[25] The recommended dosage for hyperbaric bupivacaine is 1 mg/kg 0.5% in children weighing less than 5 kg, 0.4 mg/kg in children 5 to 15 kg, and 0.3 mg/kg in children weighing more than 15 kg.

In older children, there are few indications for spinal block in view of the short duration of analgesia. The usual dosage of 1% tetracaine plus 10% dextrose is 1 mg per year of age.

Evidence-based conclusions and clinical advice

- Tetracaine 0.5% in 5% dextrose can be used for spinal anesthesia: 0.13 mL/kg (ie, 1 mg/kg) in infants weighing less than 4 kg and 0.07 mL/kg (ie, 0.5 mg/kg) in infants weighing more than 4 kg. (Evidence B3)
- Hyperbaric or isobaric bupivacaine can also be used for spinal anesthesia. The recommended dosage for hyperbaric bupivacaine is 1 mg/kg 0.5% in children weighing less than 5 kg, 0.4 mg/kg in children 5 to 15 kg, and 0.3 mg/kg in children weighing more than 15 kg. (Evidence B3)

TABLE 2. Onset and Duration of Action and Potency of Various LAs

Drug	Onset of Action	Duration of Action	Potency
Chloroprocaine	Short	1 h 30 min to 2 h	1
Lidocaine	Short	1 h 30 min to 2 h	1
Bupivacaine	Intermediate	3 h to 3 h 30 min	4
Levobupivacaine	Intermediate	3 h to 3 h 30 min	3.9
Ropivacaine	Intermediate	2 h 30 min to 3 h	3.3

- The performance of spinal anesthesia with ropivacaine can be performed in children with a dose of 0.5 mg/kg. (Evidence B3)

Caudal Block—Single Injection

The recent Pediatric Regional Anesthesia Network data reported a large variation in LA dose used in caudal blocks.[26] Indeed, the data suggest that approximately 25% of patients undergoing a caudal block received an LA dose with the potential to cause LA toxicity. Younger children seem to be at greatest risk of receiving a toxic dose. 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.[27] Some authors used more volume of diluted ropivacaine (0.15%): if the total dose is fixed, caudal analgesia with a larger volume of diluted ropivacaine provides better quality and longer duration after discharge than a smaller volume of more concentrated ropivacaine (0.125%).[28–31] In addition, ropivacaine undergoes slower systemic absorption from the caudal epidural space than bupivacaine; ropivacaine produces lower incidence of motor blockade in the early postoperative period than bupivacaine.

Evidence-based conclusions and clinical advice

- 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. (Evidence B2)

Lumbar or Thoracic Epidural

Similarly to caudal anesthesia, the use of ropivacaine 0.2% or levobupivacaine/bupivacaine 0.25% is common for lumbar or thoracic epidural in children.[32–34] 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" in order to obtain intraoperative analgesia. The buffering properties of the epidural space are important and prevent a rapid rise in concentration. The maximum dose usually used is 1.7 mg/kg ropivacaine and 1.7 mg/kg levobupivacaine and bupivacaine.[35]

Evidence-based conclusions and clinical advice

- The use of LAs for lumbar or thoracic epidural in children should not exceed a dosage of 1.7 mg/kg of ropivacaine, bupivacaine, or levobupivacaine. (Evidence B3)

Continuous Infusion Epidural Anesthesia

Epidural infusions of ropivacaine provided satisfactory pain relief in neonates and infants younger 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 to 72 hours. 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, greater than or equal to 0.35 mg/L.[35] In the first weeks of life, ropivacaine infusion should be used with more caution. Because of concerns about toxicity due to accumulation of amide LAs in infants and young children, chloroprocaine could be an alternative.[36]

Evidence-based conclusions and clinical advice

- The performance of continuous epidural anesthesia with bupivacaine/levobupivacaine can be performed with a dose of 0.2 mg/kg per hour for children younger than 3 months, 0.3 mg/kg per hour for children between 3 months and 1 year, and 0.4 mg/kg per hour for children older than 1 year. (Evidence B3)
- The performance of continuous epidural anesthesia with ropivacaine can be performed with a dose of 0.2 mg/kg per hour for children younger than 3 months, 0.3 mg/kg per hour for children between 3 months and 1 year, and 0.4 mg/kg per hour for children older than 1 year. (Evidence B3)
- The performance of continuous epidural anesthesia with chloroprocaine can be performed with a dose of 0.2 mg/kg per hour for children younger than 3 months, 0.3 mg/kg per hour for children between 3 months and 1 year, and 0.5 mg/kg per hour for children older than 1 year. (Evidence B3)

Single-Injection LA Dosage for Peripheral Nerve and Fascial Plane Blocks

The introduction of ultrasound-guided regional anesthesia has increased the use of peripheral nerve blocks in children during recent years.[37–39] Nonetheless, few publications have addressed the pharmacodynamics of LAs in children.[6] In addition, pharmacokinetic properties of LAs significantly differ between different types of blocks.[40]

Many studies have examined dose responses of single peripheral nerve blocks in pediatrics.[41–43] Nonetheless, dosages have been examined in very few block types by more than 1 study, and this limits the reliability of the findings.[6] Intercostal nerve blocks are known to have the greatest rate of reabsorption and therefore the highest potential risks of LA systemic toxicity.[44,45] Conversely, higher LA dosages (2.5 mg/kg) used for intercostal nerve blocks have resulted in plasma levels below potential toxic levels.[46]

Evidence-based conclusions and clinical advice

- The performance of ultrasound-guided upper-extremity peripheral nerve blocks (eg, axillary, infraclavicular, interscalene, supraclavicular) in children can be performed successfully and safely using a recommended LA dose of bupivacaine, levobupivacaine, or ropivacaine of 0.5 to 1.5 mg/kg. (Evidence B2)
- The performance of ultrasound-guided lower-extremity peripheral nerve blocks (eg, femoral, sciatic, popliteal, adductor canal) can be performed successfully and safely using a recommended LA dose of bupivacaine or ropivacaine of 0.5 to 1.5 mg/kg. (Evidence B2)
- The performance of ultrasound-guided fascial plane blocks (eg, rectus sheath, transversus abdominis plane block, fascia iliaca) can be performed successfully and safely using a recommended LA dose of bupivacaine or ropivacaine of 0.25 to 0.75 mg/kg. (Evidence B1)

Continuous Infusion LA Dosage for Peripheral Nerve and Fascial Plane Blocks

Very limited data are available regarding plasma levels associated with continuous infusions through peripheral nerve block catheters in children. Safety data regarding both short- and long-term uses of continuous infusions have been published, using different LAs and infusion rates, including the use of ambulatory infusions following hospital discharge.[47] No incidence of local anesthetic systemic toxicity was observed during these infusions, and no neurologic complications were noted. Nonetheless, dose-ranging studies addressing efficacy of continuous LA infusions in children are rarely available.[48]

Evidence-based conclusions and clinical advice

- Continuous infusion of LA for peripheral nerve and fascial plane blocks can be safely and successfully performed with

0.2% ropivacaine or bupivacaine using an infusion dose of 0.1 to 0.3 mg/kg per hour. (Evidence B3).

Adjuvants for Neuraxial and Peripheral Blocks

Initial Word of Caution/Disclaimer: With the exception of clonidine and preservative-free morphine none of the other adjuvant agents mentioned in this practice advisory guideline are registered for spinal/epidural administration. None of the agents are registered for injection close to peripheral nerve structures. Thus, the decision to use the drugs mentioned below as adjuvants to PRA will be governed by the individual practitioner's decision, departmental policy, and the existing medicolegal situation.

Rational for Using Adjuvants: Even long-acting local anesthetics (racemic bupivacaine, levobupivacaine, and ropivacaine) have a limited duration of action (typically 4–12 hours of duration) balanced against the time period of more intense postoperative pain associated with moderate or major surgery (24–72 hours). Prolongation of the block effect in order to better match pain duration can be accomplished by the use of catheter techniques that will allow repeated bolus administration or continuous infusion of LAs. However, most pediatric surgical interventions do not merit the use of these more complicated and resource-demanding options for postoperative analgesia.[49,50] Thus, a popular alternative to achieve prolongation of a single-injection nerve block is to use adjuvant drugs that are mixed with the LAs and thereby increase the duration of the nerve block.[51,52]

Advantages associated with the use of adjuvant drugs include (1) prolong block duration and analgesic effect, (2) reduce general anesthetic requirement, (3) allow for a smooth emergence from anesthesia and a calm recovery room stay, (4) reduce the incidence of emergence delirium and shivering, (5) provide a comfortable early postoperative period in the context of ambulatory surgery that will allow early discharge from the hospital and a pain-free transfer back home.

Fundamental Requirements of Adjuvant Drugs: Fundamental requirements of adjuvant drugs include the following: (1) preferably meta-analysis data should verify the beneficial effect of the adjuvant in order to recommend routine use outside clinical trials; (2) there should be sufficient insight into the mechanism of action of the adjuvant; (3) the side effect profile should be tolerable in comparison with the use of plain LAs; (4) the adjuvant must be available as a preservative-free preparation; and (5) overall safety issues must be acceptable in animal studies.[53–57]

Evidence-Based Conclusions and Clinical Advice for Neuraxial Adjuvants

- Clonidine(1–2 μg/kg) and morphine (10–30 μg/kg) can be used intrathecally to prolong the duration of spinal blockade in children. Because toxicity data are very limited in children, the dose used should be the minimally necessary to achieve the benefits and minimize potential adverse effects. (Evidence A2)
- Racemic ketamine (0.5 mg/kg) and S-ketamine have been used as a neuraxial adjunct in children. Nevertheless, ketamine is not recommended for intrathecal use in neonates and infants because of the possible potential for enhanced neuronal apoptosis in the spinal cord. Because toxicity data are very limited in children, the dose used should be the minimally necessary to achieve the benefits and minimize potential adverse effects. (Evidence B3)
- Dexmedetomidine has been used to prolong postoperative analgesia when used as an adjunct to neuraxial blocks (ie, caudal block). Because toxicity data are very limited in children, the dose used should be the minimally necessary to achieve the benefits and minimize potential adverse effects. (Evidence A2)
- Although synthetic opioids (eg, fentanyl and sufentanil) are common as adjuvants in the context of adult epidural analgesia, there is currently lack of evidence that synthetic opioids produce any relevant effect when used as adjuvants to caudal blocks in children. Fentanyl does not potentiate the effect of either bupivacaine or ropivacaine in the context of caudal blockade. (Evidence A2).
- Corticosteroids (eg, dexamethasone) have been used in small studies in pediatric patients as a neuraxial adjuvant. Based on the current clinical evidence, the advisory committee does not recommend the use of corticosteroids as a neuraxial adjuvant in children. (Evidence B2)

Evidence-Based Conclusions and Clinical Advice for Peripheral Nerve Block Adjuvants

- Alpha-2 adrenoceptor agonists (eg, dexmedetomidine) can be used as an adjunct to prolong the duration of peripheral nerve blocks in children.[58] Because toxicity data are very limited in children, the dose used should be the minimally necessary to achieve the benefits and minimize potential adverse effects. (Evidence A1)

CONCLUSIONS

Several large multicenter studies have recently revealed a large variability in LA dosage used for the performance of regional anesthesia in children.[26,47,59] ASRA and ESRA have worked together to provide guidance to clinical practitioners given the current lack of absolute evidence. Both societies hope to decrease not only the use of potentially toxic doses, but also the use of doses that can result in lack of efficacy of regional anesthesia in children.

A practice advisory should be used only after practitioners recognize its limitations. As new data become available, it is possible that updated versions of the current guideline may be needed. Implementation of the current practice advisory has to take into consideration individual practices and health care systems. Lastly, the advisory group did not intend to cover all clinical scenarios rather than provide clinical guidance for the use of the most common regional anesthesia techniques in children.

We did not provide a detailed or prescriptive information for specific blocks. For example, studies have demonstrated that thoracic paravertebral block (as a single-injection or continuous infusion) can be successfully used in children including young infants. Published reports evaluating the pharmacokinetics of lidocaine and bupivacaine after single-injection and continuous paravertebral infusion in children demonstrated that potentially high total plasma levels of bupivacaine were not uncommon in young infants after infusion of 0.25% bupivacaine at 0.25 to 0.5 mg/kg per hour. A follow-up study showed that effective postthoracotomy analgesia was still achieved with a lower concentration (bupivacaine 0.125% with epinephrine 1:400,000) and dosage (0.2 mL/kg per hour for 48 hours), but systemic accumulation still occurred, and concentrations greater than 3 μg/mL were recorded in a few infants at 48 hours.

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