Best Practice & Research Clinical Anaesthesiology 24 (2010) 309–321

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

2

Regional anaesthesia and analgesia in the neonate

Per-Arne Lönnqvist, MD, DEAA, FRCA, PhD, Professor of Paediatric Anaesthesia &; Intensive Care, Senior Consultant [a,b,*]

[a] *Section of Anaesthesiology & Intensive Care, Department of Physiology & Pharmacology, Karolinska Institute, SE-171 77 Stockholm, Sweden*
[b] *Paediatric Anaesthesia & Intensive Care, ALB/Karolinska University Hospital, SE-171 76 Stockholm, Sweden*

Keywords:
regional anaesthesia
neonatal
regional anaesthesia
local anaesthetics
regional anaesthesia
adjuncts
neonates
clonidine
ketamine

A large number of published studies have shown that the use of diverse regional anaesthetic techniques is associated with high-quality pain relief following the different types of surgery and painful procedures that are commonly performed in neonatal patients. Apart from pain, few studies have examined other outcomes in this setting. Some data suggest a benefit with regional anaesthesia. In a retrospective study, Bosenberg et al. found that the use of epidural analgesia in neonatal patients undergoing tracheo-oesophageal fistula repair resulted in a reduced need for postoperative mechanical ventilation. Furthermore, epidural analgesia was found to be associated with a significant and beneficial modification of the neuroendocrine surgical stress response after major abdominal surgery in infants when compared to postoperative morphine infusions. The use of local anaesthetics in association with neonatal circumcision has also shown a benefit as neonates not treated with eutectic mixture of lidocaine and prilocaine (EMLA) or a penile block had an exaggerated pain response to later vaccinations as compared with neonates treated with a local anaesthetic technique. Finally, safety data generated from large, prospective studies and audits clearly show that the use of paediatric regional anaesthetic techniques is associated with adequate safety also in neonatal patients. In conclusion, a large variety of local and regional anaesthetic techniques can be safely used in neonatal patients. The use of such techniques must obviously be associated with sufficient knowledge about the various

* Paediatric Anaesthesia & Intensive Care, ALB/Karolinska University Hospital, SE-171 76 Stockholm, Sweden. Tel.: +46 851774705; Fax: +46 851777265.
E-mail address: per-arne.lonnqvist@ki.se.

1521-6896/$ – see front matter
doi:10.1016/j.bpa.2010.02.012

techniques, as well as adherence to adequate dosage guidelines and other safety precautions. However, if these prerequisites are met, regional anaesthesia may offer great advantages to our smallest and most vulnerable patients.

Since the 1980s, a large number of studies and scientific data have shown that both neonates and premature babies do possess the neuro-anatomical and synaptic prerequisites to perceive nociceptive stimulation. Clinical studies by Anand and co-workers, focussing on the importance of providing adequate analgesia to our smallest patients, have clearly shown that insufficient intra- and post-operative analgesia does result in an exaggerated neuroendocrine stress response, increased morbidity and even increased mortality in the case of neonatal cardiac surgery. There is also evidence that the foetus has a similar response. It has also been shown that, compared to puncture of the non-innervated umbilical cord, intrauterine exchange transfusions performed through the innervated abdominal wall of the foetus result in a greater neuroendocrine stress response and subsequent behavioural changes.[1,2] Not only may insufficient pain relief be associated with negative short-term effects but insufficient neonatal analgesia also has long-term effects. Taddio et al. have clearly shown that neonatal boys who were circumcised without analgesia have a more pronounced pain experience to later immunisation injections, compared with boys who had received active analgesia by means of EMLA cream (EMLA, eutectic mixture of lidocaine and prilocaine).[3,4] Thus, there is no doubt that both neonates and premature babies should receive adequate pain relief for both surgical interventions as well as painful procedures outside the operating theatre, for example, in the neonatal intensive care unit (NICU).

One of the best, and may be also the safest, ways to provide high-quality analgesia is with the use of local anaesthesia, either alone or in combination with other drugs. The small size of neonatal patients does not in any manner preclude the use of local or regional anaesthetic techniques. The aim of this review is to provide clinically useful information on how to use regional anaesthesia and analgesia in a safe and effective way in neonates and premature babies.

Topical application and local infiltration

All newborn babies should undergo metabolic screening and are therefore subjected to blood sampling soon after birth. This is frequently accomplished by heel lancing, which is associated with a significant pain experience. Although not licensed for use in neonates, attempts to use EMLA cream prior to heel lancing have not produced good analgesia for this procedure.[5] A possible explanation for this may be the high skin blood flow in this area (the reason for performing sampling at this anatomical point).[6] By contrast, a recent Cochrane report has found the use of EMLA cream to have beneficial effects on pain caused by circumcision; being better than placebo but less effective than a penile nerve block.[4] Thus, although it appears that the efficacy of EMLA cream in this age group is dependent on the site of application, it can be successfully used for a number of different procedures in neonates and infants.[7,8] One must also be careful with regard to the amount of EMLA cream that is applied so as not to subject the child to the risk for symptomatic methaemoglobinaemia caused by the prilocaine component of EMLA. There are limited data describing the use of the other local anaesthetic creams (Ametop or Rapidan) in neonates and premature babies.

In neonates, the topical spray of lidocaine to the larynx and trachea can successfully minimise the nociception and haemodynamic stress response associated with airway manipulations. Since the actual spraying in these situations is often performed by the ear, nose and throat (ENT) surgeon, it is of great importance for the anaesthetist to note the concentration of the lidocaine used and limit the dose to reduce the risk of systemic toxicity. In a study by Gjonaj et al., it has been found that 8 mg kg^{-1} of lidocaine can be nebulised without reaching toxic plasma concentrations.[9]

For more localised procedures, such as cut-down for silastic catheter placement, intra-osseous needle insertion for vascular access and bone marrow aspiration, the injection of local anaesthetics at the site of the procedure is an easy but often-forgotten technique. As with other regional anaesthetic

techniques, it is important to keep to a safe total dose of local anaesthetic. One should also note that the adjunct use of adrenaline is associated with pronounced injection pain/burning and should thus best be avoided if the child is not under general anaesthesia already.

Equipment

Data from the 1996 French Language Society of Paediatric Anaesthesia (ADARPEF) study show that 50% of the complications of regional anaesthesia were due to the use of the wrong type of regional anaesthesia equipment; most often, the use of adult-sized equipment in paediatric patients.[10] Currently, age-specific regional anaesthesia equipment is commercially available. Epidural catheter kits with Touhy needles down to the size of 19–20-G as well as 24-G styletted caudal needles are now produced by various manufacturers. Further, recently, a specific kit to facilitate the use of the Tsui method (see below) has also been made commercially available. Thus, there is currently no support or rationale for not using age-adequate equipment in children.

Central nerve blocks

Spinal (intrathecal) blockade

This technique has been described in detail elsewhere in this issue. Awake spinal (intrathecal) blockade is a well-described technique to produce surgical anaesthesia mainly for inguinal hernia repair in the ex-premature child.[11] Surprisingly large amounts of local anaesthetics are necessary to produce an adequate block (0.14 ml kg^{-1} of bupivacaine 0.5%).[12] A prolongation of the block can be achieved by the addition of clonidine (1 mcg kg^{-1}).[13] The use of a spinal block technique to produce a complete spinal blockade in association with neonatal cardiac reconstructive surgery has also been recently described (with or without an intrathecal catheter that will allow the administration of top-up doses) and is reported to produce excellent conditions for this type of advanced surgery, including beneficial modification of the neuroendocrine surgical stress response.[14] This method has so far only been used in patients who are supported by extra-corporeal bypass, which provides adequate safety should excess haemodynamic reactions occur. Against this background, this technique should at present not be used outside this specific indication except as part of an approved clinical trial.[15]

Caudal blockade

This block is one of the most basic regional anaesthetic techniques in children, and is also well-suited to the smallest patient category.[16] It is one of the easiest blocks to learn with one study suggesting only 32 blocks are necessary before reaching adequate success rates.[17] A caudal block can, depending on the dose and volume of the local anaesthetic, produce adequate anaesthesia up to the mid-thoracic region and, thus, can be used either alone as an awake technique, or as a supplement to general anaesthesia for all surgical procedures from the mid-thoracic level down (Table 1). With ultrasound, it is now possible to visualise the injection of local anaesthetics in the caudal space as well as monitor the cranial spread.[18] The use of ultrasound is highly recommended in neonates who receive concomitant general anaesthesia, but is much more difficult to use in the awake and mobile baby.

Although this block can be used for almost all surgical interventions below the level of the umbilicus in neonatal babies, the use of this technique in association with neonatal inguinal hernia repair is by far the most common one.

Table 1
Caudal blockade. Levels of surgical anaesthesia in relationship to injected volume of local anaesthetic. Modified according to Armitage.[72]

Volume of caudal injectate (ml kg^{-1})	Typical surgical procedures
0.5	Urogenital + club foot surgery
1.0	Subumbilical surgery
1.25	Surgical procedures below the mid-thoracic level

The awake caudal technique is a useful alternative to general anaesthesia in ex-premature infants who often suffer from various degrees of bronchopulmonary dysplasia. Such babies often have had great difficulties to be weaned from mechanical ventilation and both parents and neonatologist frequently want to avoid the risks involved with general anaesthesia and re-intubation of the trachea. The use of the awake caudal technique will also limit the risk for postoperative apnoea in this specific patient category. However, for this to be true, the block must be carried out without the use of adjunct sedatives (e.g., midazolam, ketamine and low-concentrations sevoflurane by nasal prongs); otherwise the risk for postoperative apnoea will not be reduced as expected. Even in the case of a 'pure' awake caudal technique, these neonatal patients cannot be transferred to an ordinary ward after surgery but must remain in an neonatal intensive care unit/high dependency unit (NICU/HDU) environment overnight. This is particularly true if supplemental drugs such as ketamine or clonidine have been used as adjuncts to the local anaesthetic solution.[19]

The use of supplemental sedation, however, is often not necessary since the systemic absorption of the local anaesthetic together with loss of sensory input from the lower body usually make the child sleepy/sedated approximately 15–20 min following injection.[20] Care must be taken not to exceed the maximum dosage recommendations, particularly since these patients do not receive any sedative drugs that would usually increase the seizure threshold. The administration of 3 mg kg^{-1} of racemic bupivacaine has been shown to produce pre-toxic EEG signs in this patient category.[20] The administration of oral sucrose can also be helpful in neonates with awake caudal anaesthesia. It not only alleviates the discomfort of preoperative starvation but also has significant analgesic properties.[21]

Even if the most frequent indication for the awake caudal technique in neonates is inguinal hernia repair, this technique can also be very useful for venous catheter placement in the saphenous or femoral vein, and other lower limb procedures. One specific indication, that has proven useful in the author's experience, is to provide adequate analgesia and abdominal wall relaxation when performing an awake reduction of gastroschisis according to the Bianchi technique[22] soon after birth (unpublished data).

Epidural blockade

Since the popularisation of this technique for use in paediatric patients in the late 1980s, this technique to produce intra- and postoperative pain relief has become a standard procedure in children. Bosenberg and co-workers have been the pioneers with regard to its use in neonatal patients[23] and could show in an early study that epidural blockade drastically reduced the need for postoperative ventilation in neonates undergoing tracheo-oesophageal fistula repair.[24] Furthermore, Wolf et al. have clearly shown that the use of epidural blockade in infants undergoing major abdominal surgery results in significantly better modification of the neuroendocrine surgical stress response than postoperative intravenous morphine infusion.[25] The use of epidural analgesia may also shorten the period of postoperative paralytic ileus in small babies.[26] Large observational studies have shown that the use of epidural analgesia, even in neonates is associated with an acceptable risk–benefit profile.[27] Although the use of epidural blockade in neonates and infants has been questioned by some,[28] this method for intra- and postoperative analgesia represents one of the cornerstones of high-quality analgesia for neonates undergoing more extensive surgical interventions. Some technical aspects of neonatal epidural blockade are discussed below.

Loss-of-resistance (LOR)

The use of air for loss-of-resistance (LOR) has been much debated since the use of air has been reported to cause both intravascular air embolism as well as permanent spinal cord injury.[29–31] Although this argument is not finally settled, it has been recommended to use only saline for LOR in paediatric practice.[32]

Use of test dosing

Due to the limited size of the equipment used in small children, inadvertent intravascular placement of the epidural catheter cannot be reliably identified solely from spontaneous backflow in the catheter or from an aspiration test. There is also controversy over the utility of using an adrenaline containing test dose. The occurrence of a heart rate increase or changes in T-wave appearance on the

electrocardiograph (ECG) as a result of inadvertent intravascular administration is influenced by the inhalational anaesthetic agent used and if the child has received atropine prior to the administration of the test dose.[33] Since a negative result of the use of a test dose is not conclusive, many clinicians do not routinely use this safety precaution in children.

Insertion at the appropriate dermatomal level in relation to the surgical intervention

Of paramount importance to achieve a well-functioning epidural block is that the tip of the epidural catheter is situated at an intraspinal level that corresponds to the dermatomal centre of the surgical procedure. Thus, having the tip of the catheter at the lumbar level will not produce adequate analgesia if the patient is undergoing a thoracotomy. The most straightforward approach to get the catheter tip at the right intraspinal level is to perform the epidural puncture at the appropriate dermatomal level, for example, at Th 8 for a major upper laparotomy or at Th 5 for a posterolateral thoracotomy. However, to make this technique really reliable, it is important not to insert more than a few centimetres of the catheter into the epidural space.

Despite the low risk for major damage associated with thoracic epidural use in children[10,27] the risk for traumatic spinal cord injury does still exist, as has been demonstrated by occasional case reports.[34,35] In order to avoid even the slightest risk for traumatic cord injury, and to reduce the risk of catheter dislodgment many paediatric anaesthetists, favour alternative methods for epidural catheter insertion.

Blind caudal catheter technique

Since neonates and non-walking infants have not yet developed the adult pattern of spinal curvatures, it is possible to access the epidural space at the caudal hiatus, and then insert a predetermined length of the catheter to reach the desired spinal level. If using this technique, which was first described by Bosenberg,[36] it is important not to use a Touhy needle since it is very difficult to get the right alignment of the eye of the Touhy needle with the spinal canal. To improve the chance of success the use of a Crawford needle or a regular intravenous catheter is recommended. A very high success rate has been claimed with this blind approach, even to the extent that certain authors have suggested that radiographic verification of the catheter tip location is unnecessary.[37] However, other publications have amply shown that catheters threaded from the caudal space do not at all behave in a predictable way, and that radiographic verification is clearly indicated.[38] Although this approach is appealing due to its simplicity, the need for radiographic verification increases complexity. Note that if the tip position is suboptimal the administration of epidural morphine may be considered, as its effect is not dependent on precise anatomical administration.

The method of threading the catheter via the caudal route may have a renaissance if it proves possible to easily check the catheter tip position with the aid of high performance ultrasound imaging, something that unfortunately is not sufficiently reliable at present.

Nerve stimulation-guided technique: 'Tsui-technique'

Tsui et al. has recently described a method whereby the catheter is attached to a nerve stimulator.[39] After insertion of the catheter through the sacral hiatus into the caudal space, the current is increased to 1–10 mA. The catheter is then slowly advanced in the cranial direction in a similar manner to the blind technique described by Bosenberg. The major advantage with this technique is that the operator will be able to follow the muscular response as the tip of the catheter advances through the spinal canal (this obviously requires that the patient be not paralysed!). The tip of the catheter is advanced until muscle contractions are visible or palpable at the appropriate level for the planned surgical procedure. An unexpected muscular response will alert the clinician that the catheter is not threading as expected and the catheter is slightly withdrawn and the patient position modified and the catheter advanced again until the desired response is achieved. Tsui et al. have reported very good success rates with this technique, and a special kit for this technique is now commercially available (although being quite expensive).

Ultrasound-guided epidural technique

Recently, Willschke et al. have described an ultrasound-guided approach to perform epidural blockade in neonates and infants.[40,41] This method does provide real-time visualisation of the epidural puncture as well as catheter insertion. Despite the merits of this technique, it is technically very

demanding since it requires the help of a well-experienced ultrasound assistant ('experienced third arm'), and it is also difficult to find good working space and conditions during the performance of the block. The future will tell whether this new approach will become standard procedure or if it will be reserved for very special indications.

Peripheral nerve blocks

Peripheral nerve blocks represent a very elegant way of producing analgesia for surgery or painful procedures. However, the indications for peripheral nerve blocks in neonates are limited. One very useful indication is infraorbital nerve blocks for neonatal cleft lip surgery.[42] Ultrasound-guided ilioinguinal/iliohypogastric nerve blocks represent a relevant alternative to caudal blocks for inguinal hernia repair,[43–45] but can only be used as a supplement to general anaesthesia and not as an 'awake' technique. Other types of peripheral nerve blocks may, of coure, be used in specific instances, for example, axillary plexus block for upper limb ischaemia following arterial cannulation in premature babies[46] or transverse abdominal plane (TAP) blocks for major neonatal abdominal surgery.[47] Indications for continuous peripheral catheter techniques are rare in the neonatal population but continuous thoracic paravertebral nerve blocks can provide an alternative to epidural analgesia and may be used for unilateral surgical procedure on the trunk, for example, posterolateral thoracotomy or renal surgery.[48,49]

Wound-infiltration techniques

Local infiltration and wound instillation with local anaesthetic have been described in association with inguinal hernia repair but only produce a brief effect. In adult practice, the use of catheters in the surgical wound has recently become quite popular for a variety of surgical interventions, and recently, Tirotta et al. described the successful use of wound catheters after paediatric cardiac surgery by median sternotomy, with better pain relief, less opioid consumption and less need for sedative supplementation compared to a placebo wound infusion.[50] The study adhered to the recognised dosage guidelines, and plasma concentrations of levo-bupivacaine were found to be within safe limits. However, only infants and children older than 3 months and/or weight more than 5 kg were included in the study. Successful use of continuous wound infiltration for iliac bone grafting in older children has also recently been described.[51]

The technique of continuous wound catheters represents an attractive avenue to achieve adequate postoperative pain relief in neonates and small infants as the catheter can be placed under direct vision by the surgeon, and therefore, the risk for complications is minimised. No published data so far exist in this patient category but, at the Karolinska University Hospital, we are currently conducting studies both in term neonates as well as in premature babies undergoing ductus ligation using this technique. Preliminary results from the ductus ligation study show that the use of indwelling wound catheters reduces the duration of the supplemental morphine infusion from 4.5 to 2 postoperative days as well as lowers the total postoperative morphine requirements by more than 50% (Fig. 1). However, more data are needed to clarify if wound catheter techniques can challenge other alternatives to produce good-quality postoperative pain relief in neonatal patients.

Risk of complications and safety issues

During the early days of the more widespread use of regional anaesthetic techniques in infants and children, there were a number of case reports and case series of serious complications, including both systemic toxicity (seizures and ventricular arrhythmias), traumatic injury of the spinal cord and air embolism. These reports prompted both an Anesthesia Patient Safety Foundation (APSF) study resulting in the generation of dosage guidelines (see below) as well as a prospective study on the complications associated with the use of regional techniques in children.[10] This later study performed by ADARPEF included more than 24 000 paediatric regional blocks and found the incidence of complications to be approximately 1/1000; of which none resulted in any long-term sequalae or legal action. Of further interest, peripheral nerve blocks were not found to be associated with any major complications at all. Use of caudal blocks in the age group term–6 months of age was found to be associated with the highest incidence of complications (0.37%). A very recent follow-up study by the

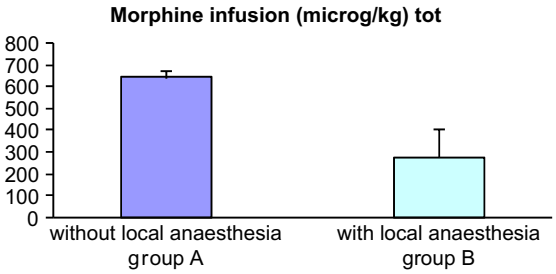

Fig. 1. Effect of wound catheter infiltration with levobupivacaine following ductus ligation in premature babies. The need for morphine infusion was significantly shorter (1,8 vs. 4,5 days) and the total morphine consumption was significantly lower in the group treated with wound catheter infiltration with levobupivacaine (274 vs 641 μg/kg).[74]

same organisation has corroborated their earlier results, reporting an overall complication rate of approximately 1/1000 blocks. An interesting trend in this new study was the use of many more peripheral nerve blocks, including continuous catheter techniques compared with central nerve blocks (Ecoffey C, ADARPEF, personal communication).

The results of a large prospective safety study concerning the use of paediatric epidural analgesia, including more than 10 000 epidural blocks, has recently been published by the Association of Paediatric Anaesthetists of Great Britain and Ireland.[27] The incidence of permanent complications that could be attributed to the use of the epidural block was approximately 1/10 000 blocks, whereas the incidence of less severe complications were found to range between 1/1000 and 1/2000. The neonatal subgroup, comprising 529 neonatal epidural blocks, had a 1.13% overall incidence of complications, which was significantly higher than in other age groups. However, most complications were due to drug errors or systemic toxicity and no complications related to catheter insertion were reported. The overall conclusion drawn from this large prospective audit was that the use of paediatric epidural analgesia, regardless of age group, is associated with an acceptable risk–benefit profile.

Although the risk for systemic toxicity has been substantially reduced following the publication of the Berde dosage recommendations, systemic toxicity can still occur after inadvertent intravascular injection. The more precise injection of local anaesthetics that follows the use of ultrasound guidance may, in fact, increase systemic absorption of the local anaesthetics if the amount is not appropriately reduced.[45] Since it is possible to reduce the volume of local anaesthetics used by at least 50% when using ultrasound guidance,[52] volume reduction is strongly recommended when using this new technique.

The infusion of a lipid emulsion to treat systemic toxicity of local anaesthetics has recently been described, and has been found surprisingly effective both in animal studies and in case reports. Excellent web-based guidelines for dose are currently available.[53,54] If regular measures to treat systemic local anaesthetic are not immediately successful, then lipid should be used (bolus of 20% lipid emulsion: 1.5 ml kg^{-1} followed by infusion of 0.25 ml kg^{-1} min^{-1}; if not successful, two additional bolus injections can be given 5 min apart). Successful use of this new treatment modality has also recently been reported in an infant.[55]

Current discussion points regarding lipid for local anaesthetic toxicity include whether this novel treatment should be started earlier in the therapeutic sequence than what is currently recommended, and if the dose of adrenaline used should be limited to a bolus injection of $\leq$10 mcg kg^{-1}. The latter issue is based on an animal study showing that higher doses of adrenaline are associated with less favourable outcome.[56] Interestingly, a recent study has suggested that lipid is only effective if bupivacaine has been administered and not if the less lipid soluble local anaesthetics ropivacaine or mepivacaine are used.[57]

Considering caudal blockade, there has been an ongoing discussion if normal sharp bevel needles can be used or if it is mandatory to use a styletted needle design. The reason for this discussion is that certain experts, for example, Dalens, claim that the use of non-styletted needles carries the risk of introducing living skin cells into the caudal space, thereby causing the risk for epidermoid growth in the caudal space. This view has been questioned by others because centres that have performed thousands of caudal blocks have never experienced this complication as well as due to the lack of well-described case reports in the literature. Recently, new data have shown that only dead stratum

Table 2
Clinically relevant key points concerning complications to regional anaesthesia in neonates and infants.

1. Always use paediatric equipment of correct size.
2. Only use saline for loss-of-resistance.
3. Remember that a negative test dose does not provide 100% security against inadvertent intravascular injection.
4. Do not exceed the maximum dosage recommendations for local anaesthetics.
5. Have Intralipid 20% immediately available in case of systemic toxicity.
6. Remember that epidural abscesses may present weeks and even months after the removal of the epidural catheter.
7. Re-evaluate the need for continuous epidural analgesia, especially in neonates and/or if the caudal insertion approach has been used, after 48 h in order to minimise the risk for systemic toxicity and infection. Continue only if the risk-benefit analysis shows that the use of continuous epidural analgesia is clearly in the best interest of the patient.

corneum cells may be carried during the use of a normal sharp bevel needle.[58] This does infer that the risk of epidermoid growth is negligible if using a non-styletted needle. Despite this recent reassuring report, it is still recommended to use the commercially available styletted caudal needles when performing caudal blocks in neonates.

Some relevant clinical key points regarding potential complications are listed in Table 2.

Dosage recommendations

When paediatric regional anaesthesia, and especially continuous epidural techniques, became popular during the late 1980s, no consensus existed regarding dosage guidelines. This resulted in a number of case reports of systemic toxicity, especially in the context of continuous infusion techniques. As a result of this, an APSF sponsored study was performed in the US. In this study, all children who had systemic toxicity had infusion rates in excess of 0.5 mg kg^{-1} h^{-1} of racemic bupivacaine.[59] Based on the results of this study, guidelines were issued for the safe dosage of racemic bupivacaine (Table 3).[59] Following the introduction of these guidelines, the incidence of systemic toxicity of local anaesthetics is more unusual, although toxicity due to inadvertent intravascular injection still occurs. However, it should be pointed out that using the maximum recommended dosage of racemic bupivacaine for continuous epidural infusions in neonates may result in borderline toxic plasma levels of bupivacaine, and infusions in excess of 48 h should only be used in infants who are judged to have considerable benefit of their continuous regional anaesthetic block.[60]

Since the introduction of the guidelines for racemic bupivacaine, new long-acting local anaesthetics (e.g., ropivacaine and levo-bupivacaine) have been introduced and some pharmacokinetic data are now available for these new agents in neonatal patients. Both these drugs are associated with a larger safety margin regarding systemic toxicity and are also associated with less motor blockade, both distinct advantages compared to racemic bupivacaine. With regard to the choice of ropivacaine or levo-bupivacaine, no decisive differences exist for paediatric use and the choice is up to personal preference or market availability.

In studies by Bosenberg et al., it has been shown that a caudal bolus injection of 3 mg kg^{-1} of ropicavaine or a continuous epidural infusion of 0.2–0.4 mg kg^{-1} h^{-1} of the same drug was clinically effective and did not result in excessive plasma levels of the drug.[61,62] Relevant pharmacokinetic information with regard to the use of levo-bupivacaine in neonates and small infants has also been

Table 3
Maximum doses of racemic bupivacaine, modified according to Berde.[59] Although it may be possible to use slightly higher doses of levo-bupivacaine or ropivacaine the author still recommends not exceeding the maximum doses outlined for racemic bupivacaine.

Bolus injection	
Neonates	1.5–2.0 mg kg^{-1}
Children	2.5 mg kg^{-1}
Continuous infusion	
Neonates	0.2 mg kg^{-1} h^{-1}
Children	0.4 mg kg^{-1} h^{-1}

published.[63] However, even if these new drugs appear to have a lower potential for systemic toxicity, it is still recommended not to exceed the maximum dosage limits as outlined by Berde.[59]

Local anaesthetics and adjunct drugs

The use of adjunct drugs to prolong and enhance postoperative analgesia is common in paediatric regional anaesthesia.[64,65] In a relatively recent survey, Saunders report that approximately 60% of UK paediatric anaesthetists routinely use adjunct drugs in combination with local anaesthetics for caudal blocks with ketamine and clonidine being the most commonly used.[64] The common use of adjunct drugs outside the UK has also recently been confirmed by data from Eich and Strauss.[65] In patients outside the neonatal age group, the use of a caudal block with a combination of S-ketamine and clonidine in saline (no local anaesthetics used) has been reported to produce good quality of postoperative analgesia during the first 24 h following inguinal hernia repair.[66]

While clonidine and ketamine represent the most commonly used adjunct drugs to enhance the effect of caudal blockade (Table 4), the use of other drugs has also been described. Unfortunately, the use of opioids has a questionable efficacy (with the only exception being preservative-free morphine) and opioids are also associated with a high incidence of side effects (e.g., PONV, pruritus and paralytic ileus), making their routine use highly debatable.[67] Like all new drugs, or new modes of drug delivery, the use of adjunct drugs should only be used routinely once there is good evidence for efficacy and safety.

In ex-premature babies scheduled for inguinal hernia repair, an awake regional technique (i.e., spinal or caudal blockade) is often used and advocated to avoid general anaesthesia and endotracheal intubation. In this setting, clonidine has been used to extend the duration of the block as well as to enhance postoperative analgesia.[13,19] However, the use of an awake regional technique in ex-premature babies does not rule out the risk of postoperative apnoea.[19] Thus, such patients must postoperatively be cared for in an environment that allows close supervision and monitoring during at least the first postoperative night even if only plain local anaesthetics are used. There are no data on how the use of clonidine influences the risk of apnoea.

No data with regard to adjunct use of drugs for continuous epidural analgesia or peripheral nerve blocks are currently available in the neonatal surgical population, but data from older children show that the adjunct use of clonidine for epidural analgesia is beneficial[68,69] as is the adjunct use of clonidine in peripheral nerve blocks.[70]

The evidence base for neonatal regional anaesthesia

A large number of published studies have shown that the use of diverse regional anaesthetic techniques is associated with high-quality pain relief following the different types of surgery and

Table 4
Adjunct drugs used to enhance the effects of local anaesthetics in children; from Mazoit & Lönnqvist.[73]

	Dose
Morphine	
Caudal/epidural bolus	33–50 mcg/kg
Fentanyl	
Caudal/epidural bolus	1.0–1.5 mcg/kg
Epidural infusion	5 mcg kg^{-1} 24 h^{-1}
Sufentanil	
Epidural bolus	0.6 mcg/kg
Epidural infusion	2 mcg kg^{-1} 24 h^{-1}
Clonidine	
Caudal/epidural bolus	1–2 mcg/kg
Epidural infusion	$\geq$0.1 mcg kg^{-1} h^{-1}
Ketamine	
Caudal bolus, racemic ketamine	0.25–0.5 mg/kg
Caudal bolus, S(+) ketamine	0.5–1.0 mg/kg

painful procedures that are commonly performed in neonatal patients. Apart from pain, few studies have examined other outcomes in this setting. Some data suggest a benefit with regional anaesthesia. In a retrospective study, Bosenberg et al. found that the use of epidural analgesia in neonatal patients undergoing tracheo-oesophageal fistula repair resulted in a reduced need for postoperative mechanical ventilation.[24] Furthermore, epidural analgesia was found to be associated with a significant and beneficial modification of the neuroendocrine surgical stress response after major abdominal surgery in infants when compared with postoperative morphine infusions.[25] The use of local anaesthetics in association with neonatal circumcision has also shown a benefit as neonates not treated with EMLA or a penile block had an exaggerated pain response to later vaccinations as compared with neonates treated with a local anaesthetic technique.[3,71] Finally, safety data generated from large, prospective studies and audits[10,27] clearly show that the use of paediatric regional anaesthetic techniques is associated with adequate safety also in neonatal patients.

In conclusion, a large variety of local and regional anaesthetic techniques can be safely used in neonatal patients. The use of such techniques must obviously be associated with sufficient knowledge about the various techniques, as well as adherence to adequate dosage guidelines and other safety precautions. However, if these prerequisites are met, regional anaesthesia may offer great advantages to our smallest and most vulnerable patients.

Practice points

- Regional anaesthetic techniques can be used in all paediatric age groups including neonates and premature babies.
- Both central and peripheral nerve-blocking techniques are associated with adequate safety if performed according to established practice.
- As in adult regional anaesthesia practice, the current trend in paediatrics is to more frequently use peripheral nerve blocking techniques as compared with central approaches, including the use of continuous catheter techniques.
- The use of ultrasound guidance offers clear advantages when used in association with most peripheral nerve-blocking techniques. The advantages, when used in association with central nerve blocks, are less clear at present.
- Clonidine can be used as an adjunct both to central and peripheral nerve blocks.
- An emerging trend in paediatric regional anaesthesia is the use of wound catheter techniques.

Research agenda

- Regional anaesthetic techniques should be compared with general anaesthesia in premature babies and neonates to investigate if regional techniques may prove beneficial with regard to the currently much-discussed issue of apoptosis.
- Regional anaesthetic techniques should be compared to other methods of postoperative analgesia in neonatal surgery with regard to clinically significant differences in morbidity, mortality and length of hospital stay.
- Further studies comparing central versus peripheral nerve-blocking techniques concerning quality of analgesia, incidence of side effects and risk of potential complications are clearly indicated.
- Further adjuncts to local anaesthetics should be investigated for use in children and neonates following adequate safety and efficacy trials performed in animals and adults.

Conflict of interest statement

None.

References

1. Wolf AR. Pain, nociception and the developing infant. *Paediatric Anaesthesia* 1999; **9**(1)**:** 7–17.
2. White MC & Wolf AR. Pain and stress in the human fetus. *Best Practice & Research. Clinical Anaesthesiology* 2004 Jun; **18**(2)**:** 205–220.
*3. Taddio A, Katz J, Ilersich AL & Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet* 1997 Mar 1; **349**(9052)**:** 599–603.
4. Brady-Fryer B, Wiebe N & Lander JA. Pain relief for neonatal circumcision. *Cochrane Database of Systematic Reviews (Online)* 2004 Oct 18; (4). CD004217.
5. Larsson BA, Jylli L, Lagercrantz H & Olsson GL. Does a local anaesthetic cream (EMLA) alleviate pain from heel-lancing in neonates? *Acta Anaesthesiologica Scandinavica* 1995 Nov; **39**(8)**:** 1028–1031.
6. Larsson BA, Norman M, Bjerring P et al. Regional variations in skin perfusion and skin thickness may contribute to varying efficacy of topical, local anaesthetics in neonates. *Paediatric Anaesthesia* 1996; **6**(2)**:** 107–110.
7. Weise KL & Nahata MC. EMLA for painful procedures in infants. *Journal of Pediatric Health Care* 2005 Jan–Feb; **19**(1)**:** 42–47.
8. Lehr VT & Taddio A. Topical anesthesia in neonates: clinical practices and practical considerations. *Seminars in Perinatology* 2007 Oct; **31**(5)**:** 323–329.
9. Gjonaj ST, Lowenthal DB & Dozor AJ. Nebulized lidocaine administered to infants and children undergoing flexible bronchoscopy. *Chest* 1997 Dec; **112**(6)**:** 1665–1669.
*10. Giaufré 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. *Anesthesia and Analgesia* 1996 Nov; **83**(5)**:** 904–912.
11. Lederhaas G. Spinal anaesthesia in paediatrics. *Best Practice & Research. Clinical Anaesthesiology* 2003 Sep; **17**(3)**:** 365–376.
12. Kachko L, Simhi E, Tzeitlin E et al. Spinal anesthesia in neonates and infants - a single-center experience of 505 cases. *Paediatric Anaesthesia* 2007 Jul; **17**(7)**:** 647–653.
13. Rochette A, Raux O, Troncin R et al. Clonidine prolongs spinal anesthesia in newborns: a prospective dose-ranging study. *Anesthesia and Analgesia* 2004 Jan; **98**(1)**:** 56–59.
14. Humphreys N, Bays SM, Parry AJ et al. Spinal anesthesia with an indwelling catheter reduces the stress response in pediatric open heart surgery. *Anesthesiology* 2005 Dec; **103**(6)**:** 1113–1120.
15. Bösenberg A. Neuraxial blockade and cardiac surgery in children. *Paediatric Anaesthesia* 2003 Sep; **13**(7)**:** 559–560.
16. Jöhr M, Seiler SJ & Berger TM. Caudal anesthesia with ropivacaine in an awake 1,090-g baby. *Anesthesiology* 2000 Aug; **93**(2)**:** 593.
*17. Schuepfer G, Konrad C, Schmeck J et al. Generating a learning curve for pediatric caudal epidural blocks: an empirical evaluation of technical skills in novice and experienced anesthetists. *Regional Anesthesia and Pain Medicine* 2000 Jul–Aug; **25**(4)**:** 385–388.
18. Roberts SA, Guruswamy V & Galvez I. Caudal injectate can be reliably imaged using portable ultrasound–a preliminary study. *Paediatric Anaesthesia* 2005 Nov; **15**(11)**:** 948–952.
19. Breschan C, Krumpholz R, Likar R et al. Can a dose of 2 microg.kg(-1) caudal clonidine cause respiratory depression in neonates? *Paediatric Anaesthesia* 1999; **9**(1)**:** 81–83.
20. Breschan C, Hellstrand E, Likar R & Lönnquist PA. Early signs of toxicity and "subtoxic" conditions in infant monitoring. Bupivacaine plasma levels following caudal anesthesia. *Anaesthesist* 1998 Apr; **47**(4)**:** 290–294.
21. Masters-Harte LD & Abdel-Rahman SM. Sucrose analgesia for minor procedures in newborn infants. *The Annals of Pharmacotherapy* 2001 Jul–Aug; **35**(7–8)**:** 947–952.
22. Bianchi A, Dickson AP & Alizai NK. Elective delayed midgut reduction-No anesthesia for gastroschisis: selection and conversion criteria. *Journal of Pediatric Surgery* 2002 Sep; **37**(9)**:** 1334–1336.
23. Bösenberg AT. Epidural analgesia for major neonatal surgery. *Paediatric Anaesthesia* 1998; **8**(6)**:** 479–483.
*24. Bösenberg AT, Wiersma R & Hadley GP. Oesophageal atresia: caudo-thoracic epidural anesthesia reduces the need for post-operative ventilatory support. *Pediatric Surgery International* 1992; **7:** 289–291.
*25. Wolf AR, Eyres RL, Laussen PC et al. Effect of extradural analgesia on stress responses to abdominal surgery in infants. *British Journal of Anaesthesia* 1993 Jun; **70**(6)**:** 654–660.
26. Hoehn T, Jetzek-Zader M, Blohm M & Mayatepek E. Early peristalsis following epidural analgesia during abdominal surgery in an extremely low birth weight infant. *Paediatric Anaesthesia* 2007 Feb; **17**(2)**:** 176–179.
*27. Llewellyn N & Moriarty A. The national pediatric epidural audit. *Paediatric Anaesthesia* 2007 Jun; **17**(6)**:** 520–533.
28. Chalkiadis G. The rise and fall of continuous epidural infusions in children. *Paediatric Anaesthesia* 2003 Feb; **13**(2)**:** 91–93.
29. Guinard JP & Borboen M. Probable venous air embolism during caudal anesthesia in a child. *Anesthesia and Analgesia* 1993 May; **76**(5)**:** 1134–1135.
30. Schwartz N & Eisenkraft JB. Probable venous air embolism during epidural placement in an infant. *Anesthesia and Analgesia* 1993 May; **76**(5)**:** 1136–1138.
31. Flandin-Bléty C & Barrier G. Accidents following extradural analgesia in children. The results of a retrospective study. *Paediatric Anaesthesia* 1995; **5**(1)**:** 41–46.
32. Sethna NF & Berde CB. Venous air embolism during identification of the epidural space in children. *Anesthesia and Analgesia* 1993 May; **76**(5)**:** 925–927.
33. Sethna NF & McGowan Jr. FX. Do results from studies of a simulated epidural test dose improve our ability to detect unintentional epidural vascular puncture in children? *Paediatric Anaesthesia* 2005 Sep; **15**(9)**:** 711–715.
34. Kasai T, Yaegashi K, Hirose M et al. Spinal cord injury in a child caused by an accidental dural puncture with a single-shot thoracic epidural needle. *Anesthesia and Analgesia* 2003 Jan; **96**(1)**:** 65–67.

35. Allison CE, Aronson DC, Geukers VG et al. Paraplegia after thoracotomy under combined general and epidural anesthesia in a child. *Paediatric Anaesthesia* 2008 Jun; **18**(6)**:** 539–542.
36. Bösenberg AT, Bland BA, Schulte-Steinberg O et al. Thoracic epidural anesthesia via caudal route in infants. *Anesthesiology* 1988 Aug; **69**(2)**:** 265–269.
37. Gunter JB & Eng C. Thoracic epidural anesthesia via the caudal approach in children. *Anesthesiology* 1992 Jun; **76**(6)**:** 935–938.
38. van Niekerk J, Bax-Vermeire BM, Geurts JW et al. Epidurography in premature infants. *Anaesthesia* 1990 Sep; **45**(9)**:** 722–725.
39. Tsui BC, Wagner A, Cave D et al. Thoracic and lumbar epidural analgesia via the caudal approach using electrical stimulation guidance in pediatric patients: a review of 289 patients. *Anesthesiology* 2004 Mar; **100**(3)**:** 683–689.
40. Willschke H, Marhofer P, Bösenberg A et al. Epidural catheter placement in children: comparing a novel approach using ultrasound guidance and a standard loss-of-resistance technique. *British Journal of Anaesthesia* 2006 Aug; **97**(2)**:** 200–207.
41. Willschke H, Bosenberg A, Marhofer P et al. Epidural catheter placement in neonates: sonoanatomy and feasibility of ultrasonographic guidance in term and preterm neonates. *Regional Anesthesia and Pain Medicine* 2007 Jan–Feb; **32**(1)**:** 34–40.
42. Bösenberg AT & Kimble FW. Infraorbital nerve block in neonates for cleft lip repair: anatomical study and clinical application. *British Journal of Anaesthesia* 1995 May; **74**(5)**:** 506–508.
43. Willschke H, Marhofer P, Bösenberg A et al. Ultrasonography for ilioinguinal/iliohypogastric nerve blocks in children. *British Journal of Anaesthesia* 2005 Aug; **95**(2)**:** 226–230.
*44. Weintraud M, Marhofer P, Bösenberg A et al. Ilioinguinal/iliohypogastric blocks in children: where do we administer the local anesthetic without direct visualization? *Anesthesia and Analgesia* 2008 Jan; **106**(1)**:** 89–93.
*45. Weintraud M, Lundblad M, Kettner SC et al. Ultrasound versus landmark-based technique for ilioinguinal-iliohypogastric nerve blockade in children: the implications on plasma levels of ropivacaine. *Anesthesia and Analgesia* 2009 May; **108**(5)**:** 1488–1492.
46. Breschan C, Kraschl R, Jost R et al. Axillary brachial plexus block for treatment of severe forearm ischemia after arterial cannulation in an extremely low birth-weight infant. *Paediatric Anaesthesia* 2004 Aug; **14**(8)**:** 681–684.
47. Bielsky A, Efrat R & Suresh S. Postoperative analgesia in neonates after major abdominal surgery: 'TAP' our way to success!. *Paediatric Anaesthesia* 2009 May; **19**(5)**:** 541–542.
48. Karmakar MK, Booker PD, Franks R et al. Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants. *British Journal of Anaesthesia* 1996 Jun; **76**(6)**:** 811–815.
49. Berta E, Spanhel J, Smakal O et al. Single injection paravertebral block for renal surgery in children. *Paediatric Anaesthesia* 2008 Jul; **18**(7)**:** 593–597.
50. Tirotta CF, Munro HM, Salvaggio J et al. Continuous incisional infusion of local anesthetic in pediatric patients following open heart surgery. *Paediatric Anaesthesia* 2009 Jun; **19**(6)**:** 571–576.
51. Ouaki J, Dadure C, Bringuier S et al. Continuous infusion of ropivacaïne: an optimal postoperative analgesia regimen for iliac crest bone graft in children. *Paediatric Anaesthesia* 2009 Sep; **19**(9)**:** 887–891.
52. Willschke H, Bösenberg A, Marhofer P et al. Ultrasonographic-guided ilioinguinal/iliohypogastric nerve block in pediatric anesthesia: what is the optimal volume? *Anesthesia and Analgesia* 2006 Jun; **102**(6)**:** 1680–1684.
53. http://lipidrescue.squarespace.com.
54. http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf.
55. Shah S, Gopalakrishnan S, Apuya J et al. Use of Intralipid in an infant with impending cardiovascular collapse due to local anesthetic toxicity. *Journal of Anesthesia* 2009; **23**(3)**:** 439–441.
56. Hiller DB, Gregorio GD, Ripper R et al. Epinephrine impairs lipid resuscitation from bupivacaine overdose: a threshold effect. *Anesthesiology* 2009 Sep; **111**(3)**:** 498–505.
57. Zausig YA, Zink W, Keil M et al. Lipid emulsion improves recovery from bupivacaine-induced cardiac arrest, but not from ropivacaine- or mepivacaine-induced cardiac arrest. *Anesthesia and Analgesia* 2009 Oct; **109**(4)**:** 1323–1326.
58. Guldogus F, Baris YS, Baris S et al. Comparing tissue coring potentials of hollow needles without stylet and caudal needles with stylet: an experimental study. *European Journal of Anaesthesiology* 2008 Jun; **25**(6)**:** 498–501.
59. Berde CB. Toxicity of local anesthetics in infants and children. *The Journal of Pediatrics* 1993 May; **122**(5 Pt 2)**:** S14–S20.
60. Larsson BA, Lönnqvist PA & Olsson GL. Plasma concentrations of bupivacaine in neonates after continuous epidural infusion. *Anesthesia and Analgesia* 1997 Mar; **84**(3)**:** 501–505.
61. Bösenberg AT, Thomas J, Lopez T et al. Plasma concentrations of ropivacaine following a single-shot caudal block of 1, 2 or 3 mg/kg in children. *Acta Anaesthesiologica Scandinavica* 2001 Nov; **45**(10)**:** 1276–1280.
62. Bösenberg AT, Thomas J, Cronje L et al. Pharmacokinetics and efficacy of ropivacaine for continuous epidural infusion in neonates and infants. *Paediatric Anaesthesia* 2005 Sep; **15**(9)**:** 739–749.
63. Chalkiadis GA & Anderson BJ. Age and size are the major covariates for prediction of levobupivacaine clearance in children. *Paediatric Anaesthesia* 2006 Mar; **16**(3)**:** 275–282.
64. Sanders JC. Paediatric regional anaesthesia, a survey of practice in the United Kingdom. *British Journal of Anaesthesia* 2002 Nov; **89**(5)**:** 707–710.
65. Eich C & Strauss J. Prompt and powerful effect of a practice guideline on caudal additives. *Paediatric Anaesthesia* 2009 Mar; **19**(3)**:** 271–272.
*66. Hager H, Marhofer P, Sitzwohl C et al. Caudal clonidine prolongs analgesia from caudal S(+)-ketamine in children. *Anesthesia and Analgesia* 2002 May; **94**(5)**:** 1169–1172.
67. Lönnqvist PA. Adjuncts to caudal block in children–Quo vadis? *British Journal of Anaesthesia* 2005 Oct; **95**(4)**:** 431–433.
68. De Negri P, Ivani G, Visconti C et al. The dose-response relationship for clonidine added to a postoperative continuous epidural infusion of ropivacaine in children. *Anesthesia and Analgesia* 2001 Jul; **93**(1)**:** 71–76.
69. Cucchiaro G, Adzick SN, Rose JB et al. A comparison of epidural bupivacaine-fentanyl and bupivacaine-clonidine in children undergoing the Nuss procedure. *Anesthesia and Analgesia* 2006 Aug; **103**(2)**:** 322–327.
*70. Cucchiaro G & Ganesh A. The effects of clonidine on postoperative analgesia after peripheral nerve blockade in children. *Anesthesia and Analgesia* 2007 Mar; **104**(3)**:** 532–537.
71. Taddio A, Goldbach M, Ipp M et al. Effect of neonatal circumcision on pain responses during vaccination in boys. *Lancet* 1995 Feb 4; **345**(8945)**:** 291–292.

72. Armitage EN. Caudal blocks in children. *Anaesthesia* 1979; **34:** 396.
73. Mazoit JX & Lonnqvist PA. Local anaesthetics and their adjuncts. In Bingham R, Lloyd-Thomas A & Sury M (eds.). *Hatch & Sumner's textbook of paediatric anaesthesia*. 3rd edn. Hodder Arnold, 2009, pp. 211–226.
74. Bartocci M, Lundeberg S, Lönnqvist PA. Local anesthesia via subcutaneous catheter after thoracotomy in premature infants. World Congress of Pediatric Pain, Vancouver, 2006 (abstract).