Ketamine as an adjunct to caudal block in neonates and infants: is it time to re-evaluate?

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The practice of adding adjunct analgesic drugs to local anaesthetics for neuraxial block in children is common, especially with caudal blocks. The most commonly used drugs are clonidine, ketamine, and opioids. With the exception of preservative-free morphine, the support for other opioids as an adjunct to single injection caudal block is weak. Other drugs have also been used in this context but must still be regarded as experimental (e.g. neostigmine, midazolam).

Addition of preservative-free racemic ketamine or single isomeric S-ketamine to long-acting local anaesthetics in the context of caudal block prolongs analgesia, with a duration of 2.26 [95% confidence interval (95% CI): 1.53–2.98] and 5.60 (95% CI: 5.45–5.76) reported in recent meta-analyses. In fact, caudal injection of ketamine alone or combined with clonidine, without the use of local anaesthetics, can produce prolonged postoperative analgesia without apparent negative side-effects or complications in children. Is this sufficient evidence to confirm safety for spinal administration?

A lot of interest has recently focused on the issue of anaesthesia-induced neuronal apoptosis or programmed cell death in neonatal animals. Ketamine has been identified as one of the most potent drugs in this regard. Systemic doses of ketamine that produce general anaesthesia in rodents and primates also increase neuronal apoptosis, and effects vary with dose and age at exposure. However, these studies have predominantly evaluated neuronal apoptosis in the brain, particularly the cortex and hippocampus, and the potential long-term effects of such drug-induced increases in programmed cell death on cognitive outcomes.

In the light of the current debate about ketamine-induced neuronal apoptosis, the use of ketamine as an adjunct to caudal block in neonates and infants is associated with at least two different issues.

First, the dose of ketamine used to enhance the effect of local anaesthetics when performing caudal blocks in children (0.5–1.0 mg kg\(^{-1}\)) is close to that used i.v. (1–2 mg kg\(^{-1}\)) or even i.m. (4–5 mg kg\(^{-1}\)) to induce anaesthesia. As ketamine is a very lipid-soluble drug, both cerebrospinal fluid (CSF) and plasma concentrations increase rapidly after epidural injection, with much higher plasma relative to CSF concentrations than seen after injection of hydrophilic drugs such as morphine. Systemic absorption of caudally injected ketamine could potentially increase cortical apoptosis, particularly when administered in combination with general anaesthetic drugs. In addition, caudal or epidural injection of any drug given to enhance the effect of regional anaesthesia is based on the concept that this will increase the concentration of the drug in the CSF, producing a more localized effect at the spinal cord level. However, circulation of CSF from the spinal subdural space to the intracranial subdural space may also expose the brain to significant concentrations of ketamine. The potential effects of more cephalad spread were confirmed in a recent laboratory study that confirmed a lack of pro-apoptotic effects in both the spinal cord and the brain after intrathecal bupivacaine in neonatal rats.

Secondly, if ketamine-induced apoptosis has been verified for cortical neurones in young animals, it would appear logical that apoptosis could also occur in the spinal cord—but is there any current evidence for such an apoptotic action of ketamine at the spinal cord level? Recently published animal data by one of the authors clearly showed that intrathecal ketamine significantly increased apoptosis in the dorsal horn of neonatal rats. Worryingly, the dose associated with neuronal apoptosis and subsequent increased glial reactivity was similar to the dose needed to produce an anti-hyperalgesic effect. Thus, the therapeutic ratio (toxic dose/analgesic dose) of ketamine in neonatal rats was calculated to be <1.

These findings raise the question of whether this is a specific risk associated with ketamine or if this is also associated with the other drugs such as morphine and clonidine?
neonatal rats, the effect of intrathecal morphine or clonidine is very different from that of ketamine. Maximum tolerated doses of intrathecal morphine or clonidine did not increase apoptosis or produce persistent changes in sensory thresholds and the therapeutic index was >300 for both drugs.14,15 Thus, both morphine and clonidine are associated with much wider margins of safety even in the youngest age.

If you decide to use an adjunct drug in infants, should you then choose morphine or clonidine? An obvious advantage of morphine is that it does not have to be injected at the appropriate dermatomal level, thus a causal injection of morphine will also be helpful in the context of a thoracotomy or upper abdominal surgery. The disadvantages with causal morphine are the obvious potential for respiratory depression and apnoea, and also additional side-effects (e.g. itching, nausea and vomiting, urinary retention, and reduced gastrointestinal mobility).16 The beneficial effect of adding causal clonidine to local anaesthetic has been demonstrated in recent meta-analyses with prolongation of analgesia by 3.98 (95% CI: 2.84–5.13)17 and 3.68 (2.65–4.7) h18 which is similar to that reported with ketamine. The respiratory effects of clonidine are much less pronounced than those associated with causal morphine. An association between causal clonidine in neonates, particularly if born preterm, and subsequent postoperative apnoea may relate to an increased sensitivity to the sedative effects in neonates.16 Systemic administration of α-2 adrenoreceptor agonists (e.g. clonidine and dexmedetomidine) has, in the experimental setting, been shown to possess neuroprotective effects against damage caused by hypoxia–asphyxia19 and by anaesthesia-induced apoptosis in the neonatal rat.20 Although dexmedetomidine has also been administered causally, it showed no advantages over clonidine,21 and there has been limited spinal safety evaluation of this drug.22

Does age matter? Programmed cell death is a normal feature in the developing nervous system, and although it is difficult to directly extrapolate developmental stages across mammalian species, the risk of drug-induced increases in apoptosis is predominantly a feature of the neonatal period and infancy. However, there is also evidence in adult animals that epidural or intrathecal preservative-free ketamine produces histopathological change in the spinal cord.23,24 As a result, the use of causal ketamine in children of any age has been questioned.25 Concern about potential spinal toxicity has been expressed by the authors of recent ketamine meta-analyses, and the use has been declined in many European centres.1 Although causal ketamine has been given without any apparent negative side-effects or complications in children, relatively few studies include follow-up beyond the immediate postoperative period. Only four studies, evaluating a total of 90 children receiving causal ketamine, included neurological evaluation at 6–8 weeks, and only one study described the assessment in detail.26 As a result, only major neurological problems are likely to be detected and subtle changes could be missed, particularly in neonates and infants who cannot describe sensory changes and who are not yet walking.

Anaesthetists are required to evaluate the relative risks and benefits of techniques, interventions, and drugs for each individual patient on a daily basis. Clinical practice guidelines provide access to current best evidence, but there are few controlled trials in neonates and infants, and many drugs have not been specifically evaluated for use by different routes in children. There is no doubt that systemic ketamine has specific advantages in some clinical scenarios (e.g. induction of anaesthesia in neonates or children with cardiac compromise), or when alternative treatment options are limited (e.g. providing additional analgesia for children with severe pain due to chemotherapy-induced mucositis). Similarly, regional analgesia plays an important role in effective management of perioperative pain in children of all ages, and the documented rate of serious neurological complications is low. However, regional techniques deliver relatively high concentrations of drugs in close proximity to the cord, and the developing spinal cord may be particularly susceptible to adverse effects. Further advances in this field require both preclinical and clinical initiatives, and will be dependent on additional research funding. Additional systematic preclinical studies evaluating dose-related effects at a range of developmental ages, preferably in more than one species, and with appropriate short- and long-term outcomes, will strengthen evidence for the comparative neurotoxicity of current and new spinal analgesics. These preclinical safety data are an important component of informed consent for both clinical trials and daily practice. Demonstration of safety in clinical studies requires more detailed and longer-term evaluation of neurological outcomes in larger groups of children. Further consensus about the criteria for using different spinal adjuvants in children is required, but if there is a choice of analgesics with similar efficacy, it seems prudent to use agents with the widest demonstrable safety margin. Current data suggest that clonidine and morphine have less adverse effects on the developing spinal cord than ketamine, and this information can further inform clinical choice of causal adjuvant, particularly when considering administration in neonates and infants.

Declaration of interest

None declared.

References


EDITORIAL III

Cancer biology, analgesics, and anaesthetics: is there a link?

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The incidence of cancer continues to increase, despite considerable investment in prevention.1 Additionally, with improved oncol ogical treatments, more people are living with, or being cured of, cancer, and many of these will have disease or treatment-related chronic pain, requiring analgesia.2 3 Currently, there is much interest in how analgesics and anaesthetics may impact on cancer biology (especially cancer recurrence and metastases) and consequently on survival.4 There are at least two areas of particular interest: first, how regional techniques or specific general anaesthetics used for cancer surgery may impact long-term survival, and secondly, how both endogenous and exogenous opioids may modulate cancer biology. It is essential to understand the possible mechanisms of these potential interactions so that patients may be given the best chance of pain-free survival.