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Double-blind randomized controlled trial of caudal *versus* intravenous S(+)-ketamine for supplementation of caudal analgesia in children

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Background. The postoperative analgesic efficacy of S(+)-ketamine after caudal or i.v. administration following sub-umbilical surgery in children was studied to investigate its principal site of analgesic action.

Methods. Sixty children undergoing caudal block during general anaesthesia for hernia repair or orchidopexy were prospectively randomized to one of three groups: the bupivicaine group received plain bupivacaine 0.25% 1 ml kg^{-1}; the caudal ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} with S(+)-ketamine 0.5 mg kg^{-1}; the i.v. ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} plus S(+)-ketamine 0.5 mg kg^{-1} i.v.. Postoperative measurements included analgesic requirements and modified objective pain score for the first 24 h.

Results. The median time to first analgesia was significantly longer in the caudal ketamine group (10 h) than in the i.v. ketamine (4.63 h) or bupivacaine (4.75 h) groups (P=0.01). Significantly fewer doses of analgesia were required over the first postoperative 24 h by subjects in the caudal ketamine group (median 1) compared with the i.v. ketamine (median 2) or bupivacaine (median 2.5) groups (P<0.05). There was no difference between the groups in the incidence of postoperative nausea and vomiting or psychomotor reactions.

Conclusions. We have demonstrated that the addition of caudal S(+)-ketamine to bupivacaine prolongs the duration of postoperative analgesia. However, the same dose of i.v. S(+)-ketamine combined with a plain bupivacaine caudal provides no better analgesia than caudal bupivacaine alone, indicating that the principal analgesic effect of caudal S(+)-ketamine results from a local neuroaxial rather than a systemic effect.

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Caudal analgesia with bupivacaine is commonly used in paediatric surgery where the operative site is sub-umbilical.[1] However, a single injection has a short duration of action and more than 60% of children undergoing orchidopexy with this technique require further analgesia during the postoperative period.[2]

Caudal ketamine has been shown to prolong the duration of postoperative analgesia in children undergoing orchidopexy[3] and inguinal herniotomy.[4] Despite numerous published reports of the safe use of racemic ketamine, this substance has not been adopted widely, because of the potential neurotoxicity of preservative agents contained in commercially available preparations.[5] However, S(+)-ketamine, one of two enantiomers of racemic ketamine, has twice the analgesic potency of the racemate[6] and is available as a preservative-free drug which has potential for epidural administration.

At anaesthetic doses, systemic administration of ketamine has been limited by undesirable emergence phenomenon, psychomimetic reactions and cardiovascular stimulating properties. However, sub-anaesthetic i.v. doses of ketamine can provide an adjunct to systemic opioid analgesia with few side-effects,[7 8] though we have been unable to demonstrate this in children following appendicectomy.[9]

Although there has been one study comparing caudal with i.m. S(+)-ketamine,[10] we are unaware of any studies comparing caudal with i.v. S(+)-ketamine. We proposed

Table 1 Patient characteristics. Results are median (interquartile range) or numbers

	Bupivacaine group	Caudal ketamine group	I.V. ketamine group
Age (months)	25 (14.3–41)	24 (18–46)	15.5 (8.3–23.8)
Weight (kg)	13 (11.8–14.7)	13.8 (11–16.7)	10 (8.6–14.1)
Procedure (orchidopexy/hernia repair)	11/9	9/10	14/6
Duration of surgery (min)	37 (20–43)	28 (22–36)	34 (25–40)

to investigate the postoperative analgesic efficacy of low-dose S(+)-ketamine administered either caudally or i.v. to supplement a plain bupivacaine caudal during sub-umbilical surgery in children in order to investigate the site of analgesic action.

Patients and methods

The study was approved by the local ethics committee and after obtaining written and informed parental consent, we recruited 60 children aged 3 months to 6 yr in a prospective, randomized, double-blind study. Any child for whom there was a contraindication to caudal block was not studied. Children undergoing day-case hernia repair or orchidopexy were allocated randomly, using sealed envelopes, to one of three groups for caudal block: the bupivicaine group received plain bupivacaine 0.25% 1 ml kg^{-1}; the caudal ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} with S(+)-ketamine 0.5 mg kg^{-1}; the i.v. ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} plus (+)-ketamine 0.5 mg kg^{-1} i.v.. Drugs were prepared by a person not otherwise involved in the study.

All children received paracetamol 20 mg kg^{-1} as premedication, and Ametop cream to the dorsum of the hand at least 20 min before surgery. Induction of anaesthesia was with either propofol 3–4 mg kg^{-1} or inhalational with sevoflurane 8%, followed by placement of a laryngeal mask airway. Anaesthesia was maintained with isoflurane 1.5–2.0% and nitrous oxide 70% in oxygen.

A caudal block was then established under aseptic conditions with the child in the left lateral position. Full monitoring was used throughout the anaesthetic period. Each child was given diclofenac 1 mg kg^{-1} *per rectum* intraoperatively. No opioids or other analgesics were administered intraoperatively. In the recovery ward, normal observations were taken every 15 min until discharge to the ward. The duration of motor blockade was assessed by determining when patients began to move their legs. The time of first micturition was noted. Assessments of the level of sedation were made at 1, 2 and 4 h, using an objective score based on eye opening (eyes open spontaneously=0; eyes open in response to verbal stimulation=1; eyes open in response to physical stimulation=2).

The efficacy of postoperative analgesia was documented using the modified objective pain score (OPS) for the assessment of postoperative pain and by duration of analgesia after caudal block. The OPS is an observational pain scoring system which has been validated for use by parents.[11] The score uses five criteria: crying, agitation, movement, posture and localization of pain. Each criterion scores from 0 to 2 to give a total score of 0–10. Duration of analgesia was defined as the time between caudal injection of the drug and first administration of postoperative analgesia. If analgesia was not required within the 24 h observation period, duration of analgesia was counted as 24 h.

Analgesia was given to children when their OPS reached 4 or more and consisted of paracetamol 15 mg kg^{-1} by mouth every 4 h as required. All assessments in the hospital were performed by observers who were unaware of the mixture used to provide caudal epidural blockade.

After discharge 4–6 h after surgery, parents were asked to assess the child regularly and give analgesia if the OPS reached 4 or more. Parents were contacted by telephone 24 h after surgery to determine the analgesic requirements at home, the timing of micturition and any evidence of nightmares, hallucinations or odd behaviour. The total requirement for postoperative analgesia in the 24 h period was noted.

Power analysis for duration of analgesia was calculated using data from previous studies. Assuming a 100% difference exists between the ketamine groups and the bupivacaine group, 20 patients in each group allows a greater than 95% chance of detecting a difference in the time to first analgesia at the usual level of significance (α=0.05). Data are presented as median and interquartile range because of the skewed distribution of the data; statistical analysis was completed using the Kruskal–Wallis test for non-parametric data.

Results

One subject in the caudal ketamine group was excluded from analysis because he did not undergo the scheduled surgery. Patient characteristics, type and duration of surgery were similar in the three groups with the exception of age in the i.v. ketamine group (Table 1). Despite the difference in age in the i.v. ketamine group, which arose by chance, there was no difference in median number of analgesic doses between the children aged 3–18 months (2 (interquartile range 1–3)), 18–36 months (2 (1–3)) and 36–71 months (1 (1–3.5)), irrespective of the group to which they were randomized (P=0.89). Additionally, the apparent difference between the groups in the type of operation was not

Table 2 Time to micturition and spontaneous leg movements. Data are median (interquartile range)

	Bupivacaine group	Caudal ketamine group	I.V. ketamine group
Time to micturition (h)	3.0 (2.1–4.0)	3.1 (2.2–4.8)	3.3 (2.6–4.6)
Duration of motor block (h)	2.2 (0.5–3.4)	2.0 (1.0–3.0)	1.8 (1.0–2.7)

Table 3 Objective pain scores after surgery. Data are median (interquartile range)

	Bupivacaine group	Caudal ketamine group	I.V. ketamine group
1 h	0 (0–2)	0 (0–0)	0 (0–2.75)
2 h	0 (0–0)	0 (0–0)	0 (0–1.75)
4 h	0 (0–0)	0 (0–0)	0 (0–0)
24 h	1 (0–3)	0 (0–1)	1 (0–1.75)

significant (P=0.35) and furthermore did not affect analgesic requirements. Children who underwent orchidopexy (n=34) showed a median time to first analgesia of 5.63 (3.56–11.06) h and the number of analgesic doses was 2 (1–3.25) compared with hernia repair (n=25) with a median time to first analgesia of 5.0 (4.1–10) h and number of analgesics of 2 (1–3) (P=0.69 and 0.88, respectively), irrespective of which treatment group they were in. Thus valid comparisons could be made between all three groups.

The median duration of action of the technique employed, as indicated by the time to first analgesia, was significantly longer in the caudal ketamine group (10 h (5.2–19)) than in the i.v. ketamine group (4.63 h (3–7.44)) or bupivacaine group (4.75 h (3.2–7.05)) (P=0.01) and there were no significant differences between the i.v. ketamine and bupivacaine groups. Significantly fewer doses of analgesia were required over the first 24 h after surgery by subjects in the caudal ketamine group (1 (1–2)) compared with the i.v. ketamine group (2 (1–3)) or bupivacaine group (2.5 (1.25–4)) (P=0.01) and once again there was no significant difference between the latter two groups. Four patients in the caudal ketamine group did not require any postoperative analgesia.

The times to first micturition and spontaneous leg movements were similar in the three groups (Table 2).

The OPS at 1, 2, 4 and 24 h after surgery are shown in Table 3. There were no significant differences between the groups at any time. There was no difference between the groups in sedation scores (median 2 in all three groups at 1, 2, 4 and 24 h) nor in the incidence of early or late vomiting (median 0 in all three groups at 1, 2, 4 and 24 h), with only seven children requiring anti-emetics. There were two children in whom vacant stares were reported by the parents before bedtime. These were short lived, having completely resolved by the next morning, and neither the parents nor the children appeared distressed by them. One child had received i.v. ketamine and the other had not received ketamine. These children had both met the strict criteria for discharge from the day surgery unit.

Discussion

Our study was designed to compare whether the addition of S(+)-ketamine to bupivacaine, when administered caudally, would prolong the duration of postoperative analgesia more than i.v. S(+)-ketamine combined with caudal bupivacaine in children undergoing orchidopexy or herniorrhaphy. The results indicate that caudal S(+)-ketamine and bupivacaine combined, prolonged postoperative analgesia by 6 h and significantly reduced the need for subsequent postoperative analgesia by more than 50% compared with caudal bupivacaine alone or i.v. S(+)-ketamine plus caudal bupivacaine.

There was no difference in postoperative sedation or in OPS between the groups at any of the time intervals studied, which is not unexpected since supplemental analgesia was given to any child whose OPS reached 4 or more. Nausea and vomiting was not a major problem in any of the groups. While motor block did occur in all groups, it was not a major problem and was shown to be no worse in the ketamine groups than in the bupivacaine group. There was no significant difference in the time to first micturition between the groups, although one child in the caudal ketamine group did have a prolonged time of 17 h.

These findings support those of other workers confirming that ketamine supplementation of bupivacaine prolongs the duration of caudal epidural blockade.[12] However, our results also demonstrate that caudal S(+)-ketamine provides more effective analgesia than i.v. S(+)-ketamine, which suggests that the analgesic effect of the caudally administered drug is caused by a direct effect on the spinal cord.

Ketamine, a derivative of phencyclidine, works at a number of different target sites which could explain this analgesic effect in the spinal cord. It is an antagonist at *N*-methyl-D-aspartate (NMDA) receptors, with a stereoselectivity in favour of S(+)-ketamine.[13] NMDA receptors are found throughout the central nervous system, including the lumbar spinal cord, and play an important role in nociceptive processing.[14] Analgesic effects may also result from agonist activity at mu-opioid receptors[15] and interaction with voltage-sensitive sodium channels.[16] Furthermore, the binding site of ketamine at mu-opioid receptors appears to be stereoselective for the S(+)-enantiomer.[17]

The use of caudal ketamine may elicit concern about potential neurotoxicity. No major sequelae have been reported after the use of caudal ketamine 1% in human studies. Animal studies have demonstrated the safety of intrathecal ketamine 1% after a single dose[18–20] and after multiple doses.[21] One study has claimed to show a definite neurotoxic effect of ketamine 1%[22] but those same workers subsequently demonstrated that it was the preservative chlorbutanol administered intrathecally that caused neuro-

toxicity whereas ketamine without preservative did not.[20] As far as ketamine is concerned, a review on the neurotoxicity of intrathecally administered drugs concluded that "taken together, the rat, rabbit, and primate studies with intrathecal ketamine support its safety if used without a preservative whereas the commercially available preparation of ketamine contains an untested preservative (benzethonium chloride) and cannot be recommended for intrathecal use in humans". [23]

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