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Efficacy and adverse effects of ketamine as an additive for paediatric caudal anaesthesia: a quantitative systematic review of randomized controlled trials[†]

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Editor's key points

- The role of ketamine as an adjunct to local anaesthetic for caudal block in children is gaining popularity.
- Analysis of 13 studies suggests that ketamine prolongs postoperative analgesia—time to first analgesia request.
- There was no increase in adverse effects.
- The potential role of ketamine in neurotoxicity still needs to be clarified.

Background. The aim of this quantitative systematic review was to assess the efficacy and adverse effects of ketamine added to caudal local anaesthetics in comparison with local anaesthetics alone in children undergoing urological, lower abdominal, or lower limb surgery.

Methods. The systematic search, data extraction, critical appraisal, and pooled data analysis were performed according to the PRISMA statement. All randomized controlled trials (RCTs) were included in this meta-analysis and relative risk (RR), mean difference (MD), and the corresponding 95% confidence intervals (CIs) were calculated using the Revman® statistical software for dichotomous and continuous outcomes.

Results. Thirteen RCTs (published between 1991 and 2008) including 584 patients met the inclusion criteria. There was a significant longer time to first analgesic requirements in patients receiving ketamine in addition to a local anaesthetic compared with a local anaesthetic alone (MD: 5.60 h; 95% CI: 5.45–5.76; $P<0.00001$). There was a lower RR for the need of rescue analgesia in children receiving a caudal regional anaesthesia with ketamine in addition to local anaesthetics (RR: 0.71; 95% CI: 0.44–1.15; $P=0.16$).

Conclusions. Caudally administered ketamine, in addition to a local anaesthetic, provides prolonged postoperative analgesia with few adverse effects compared with local anaesthetics alone. There is a clear benefit of caudal ketamine, but the uncertainties about neurotoxicity relating to the dose of ketamine, single *vs* repeated doses and the child's age, still need to be clarified for use in clinical practice.

Keywords: caudal; children; ketamine; regional anaesthesia

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Caudal blocks are used worldwide to provide safe and effective perioperative analgesia for paediatric patients (<12 yr) undergoing urological, lower abdominal, and lower limb surgery.[1] It has gained popularity[2] as this regional technique is easy to learn,[3] offers a high success rate,[4] and has a low incidence of major adverse events, including dural puncture or intravascular injections.[5] Single-shot caudal local anaesthetics, such as bupivacaine, ropivacaine, or levobupivacaine, provide analgesia for 4–8 h.[1 6] Therefore, several additives, including ketamine and clonidine, have been investigated to prolong postoperative analgesia. In a recent survey of paediatric caudal anaesthesia practice, more than 75% of the members of the Association of Pediatric Anesthetists of

Great Britain and Ireland (APAGBI) used drug additives including ketamine (37.5%) or clonidine (42.2%) for caudal anaesthesia.[7] However, a recent letter[8] reported a decrease in the use of caudal ketamine as an additive in Germany, Switzerland, and Austria due to potential neurotoxicity. There are conflicting results regarding the effects of caudal ketamine on the quality of analgesia, additional analgesic requirements, and length of postoperative analgesia.[9 10]

The aim of this quantitative systematic review was to assess the efficacy and adverse effects of caudally administered ketamine in addition to local analgesics in children undergoing urological, lower abdominal, or lower limb surgery.

Methods

This quantitative systematic review was performed according to the criteria of the PRISMA statement[11] and the current recommendations of the Cochrane Collaboration.[12] A systematic search was performed in the Central register of controlled trials of the Cochrane Library (to present), MEDLINE (1966 to present), EMBASE (1980 to present), and CINAHL (1981 to present). The search strategy consisted of a combination of free text words and MeSH terms: 'caudal' and 'ketamine'. There were no restrictions concerning the language of the article or publication type; reference lists of the retrieved articles were checked again for potential relevant publications.

Two authors (A.S. and D.M.P.) scanned the articles retrieved by the initial search to exclude obvious irrelevant studies and study eligibility was determined by reading the title and abstracts. Inclusion and exclusion criteria were established *a priori*, so that obviously irrelevant trials were excluded at this stage. These were: all randomized controlled trials (RCTs) investigating the efficacy and adverse effects of caudally administered ketamine in addition to local anaesthetic in comparison with local anaesthetic alone in children undergoing surgery were included in this review. The data of all participants irrespective of their age and type of surgery were considered.

Two authors (A.S. and D.M.P.) read the full-text articles and independently decided whether the study met the inclusion criteria. These authors performed the data extraction using a standardized form developed for this review, which included title, contact information of the authors, type of surgery, the dose and the type of local anaesthetic used, the use of a fixed postoperative pain medication in both study groups, the administration of a standardized postoperative nausea and vomiting (PONV) prophylaxis, the dose and type of rescue medication, and all relevant outcome data on efficacy and adverse effects mentioned. For further statistical analysis, the primary and secondary outcome data were entered into RevMan® 5.0 provided by the Cochrane Collaboration. All differences at any stage of data extraction and analysis were resolved by consulting a third author (P.K.Z.) or discussion among the authors.

A number of predefined outcomes were used. Duration of postoperative analgesia defined as the time from caudal injection until the first requirement of rescue analgesia was set as the most important primary outcome. As pain was assessed by different scoring systems, we were not able to calculate an average pain score for the included studies. However, a recent published Cochrane review[13] assumed the definition of various postoperative pain thresholds to be equivalent and therefore adequate to assess the duration of rescue analgesia. Most of the pain scales were based on a 10- or 12-point scale with 3 or 4 as pain trigger. Duration of motor block was defined as the time from injection to the first spontaneous leg movement and time to micturition was defined as the time from injection to the first spontaneous micturition.

The duration of postoperative analgesia (h) and the total number of postoperative rescue requirements were considered to be the primary outcome parameters. The number of patients requiring rescue analgesia, the duration of motor block (h), the time to micturition (h), and the number of children with adverse effects (PONV, bradycardia, hypotonia, respiratory depression, neurological complications, hallucination, delayed motor function, delayed micturition) were reported as secondary outcomes.

Two authors (A.S. and D.M.P.) performed the critical appraisal of the studies independently using standardized forms. The following items were evaluated as per the PRISMA statement:[11] random allocation, concealment of allocation, blinding technique, and description of withdrawal. The five-point Oxford scale was used to rate randomization, double-blinding, description of withdrawals, and dropouts. If the included studies described exactly the randomization or the blinding, they received another two points.[14]

Statistical analysis

If relevant data could not be analysed quantitatively, the reviewers reported the results of each single study qualitatively with the corresponding *P*-value. The relative risk (RR), mean difference (MD), and their corresponding 95% confidence intervals (95% CIs) were calculated for dichotomous and continuous outcome data, respectively, using a fixed-effect model, if there was no heterogeneity. Statistical heterogeneity was assessed with the I^2-test and assumed if an I^2-value $>30\%$ was observed. A random-effect model was used in the case of a significant heterogeneity. A significant effect of an intervention was assumed if the 95% CI did not include the value 1.0.

If continuous data were only reported as median and range, the mean was estimated as equivalent to the median, assuming that the study population was normally distributed. The standard deviation (SD) was calculated guessing that the width of the inter-quartile range would be $\sim$1.35 SD in the case of a normal distribution of outcome.[15] A sensitivity analysis was performed investigating the influence of this calculation.

Different analyses were planned to explore relevant statistical and clinical heterogeneity. A subgroup analysis investigated the influence of different types of long-lasting local anaesthetics (bupivacaine, ropivacaine, levobupivacaine), different doses of ketamine (0.25 *vs* 0.5 mg kg^{-1}), different doses of long-lasting local anaesthetics (1.5 *vs* 2.0 *vs* 2.5 mg kg^{-1}), and the different doses of paracetamol as the rescue medication. A potential publication bias was assessed using funnel plots. A sensitivity analysis was applied with respect to different methodical quality of the included trials (studies with low quality *vs* studies with high quality).

Results

The systematic search in the databases identified 221 relevant articles. After screening, 16 studies potentially met the inclusion criteria. The full-text publications of these

studies were examined in more detail. One study was excluded, because it was an abstract, which was published 1 yr later as a full-text article. Two studies[16 17] were excluded because they investigated two different local anaesthetic drug doses in the control and experimental groups (Fig. 1). The data of 13 randomized controlled studies[18–30] were included in the present meta-analysis (Table 1). A total of 844 children undergoing lower limb, lower abdominal, or uro-genital surgery were randomly assigned to receive either a local anaesthetic alone (295 children), ketamine in addition to a local anaesthetic (289 children), or a combination of a local anaesthetic with other additional drugs, including clonidine,[18 21 22] neostigmine,[23] midazolam,[23 26] and tramadol.[20 30] The number of participants within each treatment arm ranged from 15[27] to 25 children.[30] Main inclusion criteria were children between 1 and 12 yr, ASA I–II, undergoing lower limb or lower abdominal surgery. The exclusion criteria were infection at the insertion site of caudal block, a known allergy to the utilized drugs, a history of bleeding disorders, spinal or neurological diseases, or abnormalities of the sacrum. The children received no premedication and the anaesthesia was induced in the majority of cases with volatile anaesthetics. Five studies[20 25 26 29 30] reported an i.v. induction with thiopental, and two[21 28] used propofol. One study[28] used fentanyl before intubation, while all the others avoided a preoperative opioid administration. After induction of anaesthesia, a single-shot caudal was given using the common blind insertion technique through the sacrococcygeal ligament. All trials investigated long-lasting local anaesthetics: bupivacaine in two different concentrations (0.25%; 0.125%) was used in 10 trials and ropivacaine (0.2%, 0.4%) was applied in three trials.[18 22 28] Two trials[22 27] used S-ketamine as an additive to the local anaesthetic, while the other trials investigated the racemic ketamine. Five studies[20 21 23 27 29] used preservative-free ketamine, and one[25] used ketamine with the preservative benzethonium chloride. The majority of trials used a caudal ketamine dose of 0.5 mg kg^{-1}, while only one trial investigated the efficacy

of ketamine 0.25 mg kg^{-1}.[28] Inhalation anaesthesia was maintained with sevoflurane, halothane, or isoflurane; only one study[22] did not use nitrous oxide. No additional perioperative analgesics or prophylaxis of PONV were used in any trial. Oral or rectal paracetamol was given as the rescue analgesic in three different doses (10, 15, and 20 mg kg^{-1}) in a weight-related manner or as a fixed dose. The pain scales used and defined pain thresholds for the administration of rescue analgesics varied throughout the studies (Table 2). Nine studies investigated the analgesic efficacy of additional caudally administered ketamine in children undergoing ambulatory surgery. Subsequently, parents were called the day after surgery regarding possible adverse effects and the amount of rescue analgesics.

The study quality was throughout moderate to good (average Oxford score: 3–4) (Table 3). Only one[30] scored 2 Oxford points and was rated as low-quality study. All studies were RCTs; however, only four[20 24 26 29] explicitly described the allocation of concealment. All but two studies[29 30] were double-blinded (blinding of observer and parents/children). Two studies[22 24] excluded patients from their study and described the reasons for the withdrawal, but did not perform an intention-to-treat analysis.

Primary and secondary outcome data

Altogether the data of 13 trials investigating 844 children were included in this meta-analysis. One trial[19] tested two different local anaesthetics alone and one dose in combination with ketamine. Results of this study were analysed as separate groups.

Duration of postoperative analgesia (h)

Ten studies (437 children)[18–20 22 23 26 28–30] were eligible for assessment of duration of postoperative analgesia. There was a significant MD in the duration of postoperative analgesia between the experimental group receiving ketamine 0.25 or 0.5 mg kg^{-1} combined with a single dose of a local anaesthetic compared with the control group receiving a single dose of local anaesthetic alone (MD: 5.60 h; 95% CI: 5.45–5.76; $P<0.00001$) (Fig. 2). This result was influenced by a significant heterogeneity ($I^2=91\%$). However, a funnel plot showed a symmetric distribution of these results, indicating that a potential publication bias may not be responsible for the heterogeneity.

A subgroup analysis testing the influence of bupivacaine[19 20 22 23 26 29 30] (MD: 5.32 h; 95% CI: 4.23–6.41; $P<0.00001$) or ropivacaine[18 19 28] (MD: 5.71 h; 95% CI: 4.23–7.20; $P<0.00001$) ($I^2=0\%$) combined with ketamine and demonstrated a better analgesic efficacy with ropivacaine plus ketamine. A subgroup analysis investigating the possible influence of different local anaesthetic doses on the duration of analgesia showed a comparable duration of analgesia in trials investigating ketamine combined with local anaesthetics (Fig. 3). A subgroup analysis investigating the possible effect of different doses (0.25 vs 0.5 mg kg^{-1}) or racemic ketamine vs S-ketamine was not possible due to an inadequate number of trials. A sensitivity analysis
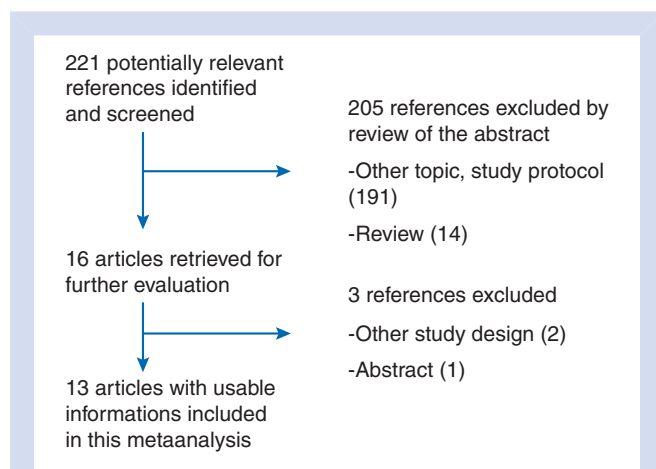
Fig 1 Flow diagram of the included and excluded studies according to the PRISMA statement.

221 potentially relevant references identified and screened

205 references excluded by review of the abstract

-Other topic, study protocol (191)

-Review (14)

16 articles retrieved for further evaluation

3 references excluded

-Other study design (2)

-Abstract (1)

13 articles with usable informations included in this metaanalysis

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Table 1 Main characteristic of the included studies testing the efficacy of additional ketamine to long-lasting local anaesthetics in caudal regional anaesthesia. $+/-$, 'not described'; $+$, 'yes';$-$, 'no'

Reference	Treatment (number of patients)	Rescue medication	Ambulatory surgery	Oxford score
Naguib and colleagues[25]	Bupivacaine 0.25% 1 ml kg^{-1} (20) Bupivacaine 0.25% 1 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (15) Saline 0.9%+ketamine 0.5 mg kg^{-1} (15)	Paracetamol supp (125 mg)	$+$	1/1/1
Cook and colleagues[21]	Bupivacaine 0.25% 1 ml kg^{-1}+epinephrine 1/200 000 (20) Bupivacaine 0.25% 1 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (20) Bupivacaine 0.25% 1 ml kg^{-1}+clonidine 2 mg kg^{-1} (20)	Paracetamol p.o. (10 mg kg^{-1})	$+$	1/1/1
De Negri and colleagues[22]	Ropivacaine 0.2% 0.75 ml kg^{-1} (25) Ropivacaine 0.2% 2 mg kg^{-1}+clonidine 2 mg kg^{-1} (20) Ropivacaine 0.2% 2 mg kg^{-1}+ketamine 0.5 mg kg^{-1} (20)	Paracetamol+kodein supp (200 mg)	$-$	1/1/1
Lee and Sanders[28]	Ropivacaine 0.2% 1.0 ml kg^{-1} (16) Ropivacaine 0.2% 1.0 ml kg^{-1}+ketamine 0.25 mg kg^{-1} (16)	Paracetamol p.o. (15 mg kg^{-1})	$+$	1/1/1
Weber and Wulf[27]	Bupivacaine 0.125% 1 ml kg^{-1} (15) Bupivacaine 0.125% 1 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (15)	Paracetamol supp (20 mg kg^{-1})	$+$	1/1/1
Akbas and colleagues[18]	Ropivacaine 0.2% 0.75 ml kg^{-1} (25) Ropivacaine 0.2% 0.75 ml kg^{-1}+clonidine 1 mg kg^{-1} (25) Ropivacaine 0.2% 0.75 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (25)	Paracetamol p.o. (15 mg kg^{-1})	$+$	1/1/1
Akbas and colleagues[19]	Bupivacaine 0.25% 0.75 ml kg^{-1} (20) Bupivacaine 0.25% 0.75 ml kg^{-1}+ ketamine 0.5 mg kg^{-1} (20) Ropivacaine 0.2% 0.75 ml kg^{-1} (20) Ropivacaine 0.2% 0.75 ml kg^{-1}+ ketamine 0.5 mg kg^{-1} (20)	Paracetamol p.o. (15 mg kg^{-1})	$+$	1/1/1
Kumar and colleagues[23]	Bupivacaine 0.25% 1 ml kg^{-1} (20) Bupivacaine 0.25% 1 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (20) Bupivacaine 0.25% 1 ml kg^{-1}+midazolam 50 mg kg^{-1} (20) Bupivacaine 0.25% 1 ml kg^{-1}+neostigmine 2 mg kg^{-1} (20)	Paracetamol p.o. (20 mg kg^{-1})	$-$	1/1/1
Pan and Rudra[26]	Bupivacaine 0.25% 1 ml kg^{-1} (20) Bupivacaine 0.25% 1 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (20) Bupivacaine 0.25% 1 ml kg^{-1}+midazolam 50 mg kg^{-1} (20) Bupivacaine 0.25% 1 ml kg^{-1}+midazolam 50 mg kg^{-1}+ketamine 0.5 mg kg^{-1} (20)	Paracetamol p.o. (20 mg kg^{-1})	$+$	2/1/1
Siddiqui and Chowdhury[29]	Bupivacaine 0.25% 1 ml kg^{-1} (20) Bupivacaine 0.25% 1 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (20) Saline 1 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (20)	Paracetamol p.o. (20 mg kg^{-1})/meperidine 1 mg kg^{-1} i.m.	$+/-$	2/0/1
Nafiu and colleagues[24]	Bupivacaine 0.125% 1 ml kg^{-1} (20) Saline 0.9%+ketamine 0.5 mg kg^{-1} (22) Bupivacaine 0.125% 1 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (20)	Paracetamol p.o. (15 mg kg^{-1})	$+$	2/1/1
Choudhuri and colleagues[20]	Bupivacaine 0.25% 0.5 ml kg^{-1} (25) Bupivacaine 0.25% 0.5 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (25) Bupivacaine 0.25% 0.5 mg kg^{-1}+tramadol 1 mg kg^{-1} (25)	Paracetamol p.o. (10 mg kg^{-1})	$+$	2/1/1
Somasundaran and Garasia[30]	Bupivacaine 0.25% 0.75 ml kg^{-1} (25) Bupivacaine 0.25% 0.75 ml kg^{-1}+ketamine 0.5 mg kg^{-1} (25) Bupivacaine 0.25% 0.75 ml kg^{-1}+tramadol 2 mg kg^{-1} (25)	Paracetamol p.o. (10 mg kg^{-1})	$+/-$	1/0/1

Table 2 Pain scales and the number of pain triggers for the administration of rescue analgesics used in the included studies

Reference	Pain scale	Pain trigger
Naguib and colleagues[25]	Three-point scale (1, none; 2, moderate; 3, severe)	'Analgesia was given as required'
Cook and colleagues[21]	Modified objective pain score (OPS)	OPS≥4
De Negri and colleagues[22]	CHEOPS	CHEOPS≥9
Lee and Sanders[28]	VAS	VAS≥4
Weber and Wulf[27]	Observational pain score (OPS) (0–10)	OPS>3
Akbas and colleagues[18]	Oucher pain scale (in hospital); modified objective pain score (OPS) (at home) (5 criteria: 0–10)	Oucher pain scale>60, OPS≥4
Akbas and colleagues[19]	Oucher pain scale (in hospital); modified objective pain score (OPS) (at home) (5 criteria: 0–10)	Oucher pain scale>60, OPS≥4
Kumar and colleagues[23]	'Five-point verbal scale' (1, asleep; 2, awake, but no pain; 3, mild pain; 4, moderate pain; 5, severe pain)	Verbal scale≥4
Pan and Rudra[26]	Verbal pain score (1, asleep; 2, awake but no pain; 3, light pain; 4, moderate pain; 5, severe pain)	Pain score≥3
Siddiqui and Chowdhury[29]	Modified TPPS (0–10)	TPPS>3
Nafiu and colleagues[24]	Modified observational pain score according to Hannallah (OPS) (0–12)	MOPS>4
Choudhuri and colleagues[20]	All India Institute of Medical Sciences (AIIMS) pain discomfort scale (5 variables 0–10)	AIIMS≥4
Somasundaran and Garasia[30]	Modified observational pain score according to Hannallah (OPS) (0–12)	MOPS>4

Table 3 Critical appraisal of included studies

| Reference	Allocation	Concealment	Blinding	Description of drop-outs	Oxford score
Naguib and colleagues[25]	Random	Not described	Observer, parents blinded (double-blind)	Yes	1/1/1
Cook and colleagues[21]	Random	Not described	Observer, parents blinded (double-blind)	Yes	1/1/1
De Negri and colleagues[22]	Random	Not described	Observer, parents blinded (double-blind)	Yes	1/1/1
Lee and Sanders[28]	Random	Not described	Observer, parents blinded (double-blind)	yes	1/1/1
Weber and Wulf[27]	Random	Not described	Observer, parents blinded (double-blind)	Yes	1/1/1
Akbas and colleagues[18]	Random	Not described	Observer, parents blinded (double-blind)	Yes	1/1/1
Akbas and colleagues[19]	Random	Not described	Observer, parents blinded (double-blind)	Yes	1/1/1
Kumar and colleagues[23]	Random	Not described	Observer, parents blinded (double-blind)	Yes	1/1/1
Pan and Rudra[26]	Random	Sealed envelopes	Observer, parents blinded (double-blind)	yes	2/1/1
Siddiqui and Chowdhury[29]	Random	Random number table	Not described	Yes	2/0/1
Nafiu and colleagues[24]	Random	Sealed envelopes	Observer, parents blinded (double-blind)	Yes	2/1/1
Choudhuri and colleagues[20]	Random	Random number table	Observer, parents blinded (double-blind)	Yes	2/1/1
Somasundaran and Garasia[30]	Random	Not described	Not described	Yes	1/0/1
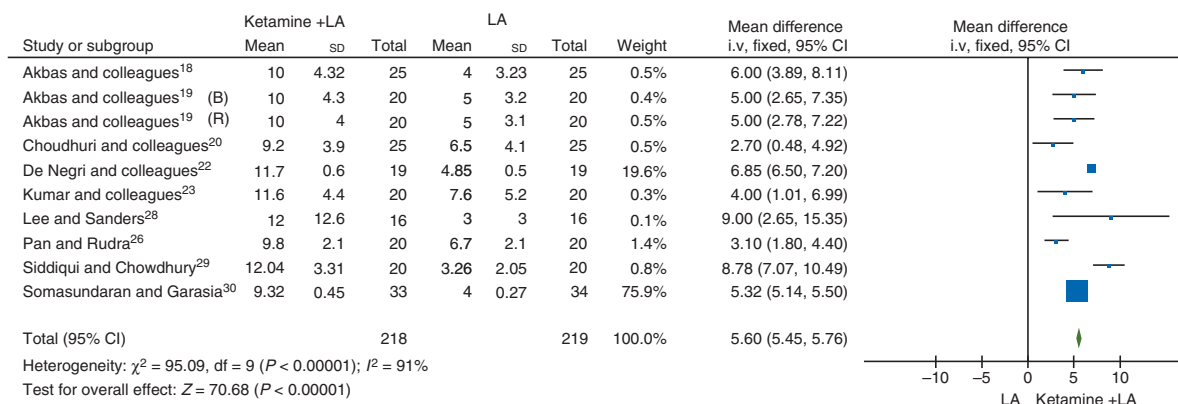
Fig 2 Pooled data analysis assessing the duration of postoperative analgesia (h) ('time until first rescue requirement').
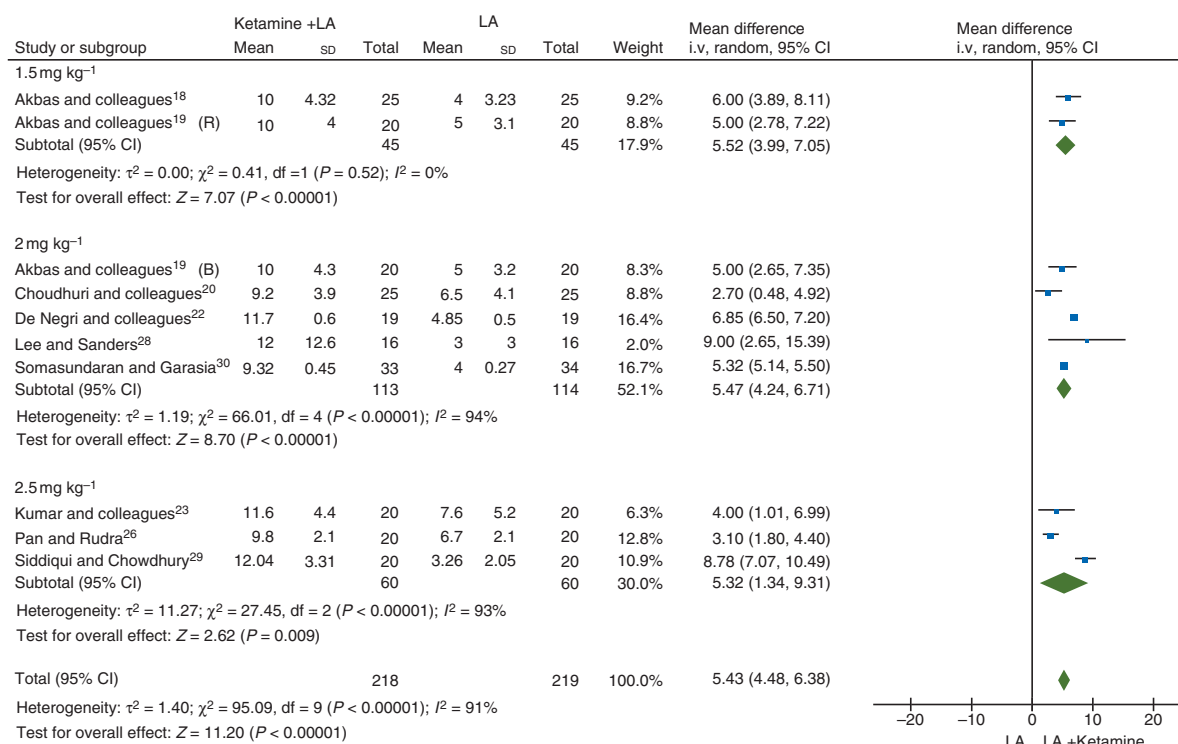

Fig 3 Pooled data analysis of the subgroup assessing the possible influence of local anaesthetic (LA) dose on the duration of postoperative analgesia (h) ('time until first rescue requirement').

investigating the influence of either low-quality studies[30] or studies not reporting median and inter-quartile range instead of mean and sd[28] showed a higher MD of 6.49 h (95% CI: 6.17–6.80; $P < 0.00001$; $I^2 = 87\%$).

Total number of postoperative rescue analgesic requirements

Eight trials[18–21 25 28 29] investigating 422 children reported the number of postoperative rescue requirements. Owing

to missing sd, a pooled data analysis was not possible and only a qualitative description of the results and corresponding *P*-values was performed (Table 4). All used paracetamol as the rescue medication in four different doses: 15,[18 19 28] 10,[20 21] 20 mg kg^{-1},[29] or 125 mg.[25] Five trials[20 21 25 28 29] reported a significant reduction of postoperative rescue requirements in children receiving ketamine in addition to local anaesthetic compared with local anaesthetic alone.

Table 4 Total number of postoperative rescue requirements in children receiving ketamine in addition to local anaesthetic (LA) in comparison with local anaesthetic alone

Reference	Rescue medication	Number of postoperative rescue requirements		*P*-value
		Ketamine+LA	LA	
Naguib and colleagues[25]	125 mg supp	1	15	<0.05
Cook and colleagues[21]	10 mg kg^{-1} p.o.	26	61	<0.01
Lee and Sanders[28]	15 mg kg^{-1} p.o.	1	3	<0.0001
Akbas and colleagues[18]	15 mg kg^{-1} p.o.	4	6	>0.05
Akbas and colleagues (Bupi)[19]	15 mg kg^{-1} p.o.	4	5	>0.05
Akbas and colleagues (Ropi)[19]	15 mg kg^{-1} p.o.	3	5	>0.05
Siddiqui and Chowdhury[29]	20 mg kg^{-1} p.o., meperidine 1 mg kg^{-1} i.m.	45	72	<0.001
Choudhuri and colleagues[20]	10 mg kg^{-1} p.o.	46	73	<0.05

Table 5 RRs and consecutive 95% CIs of adverse events after the caudal administration of ketamine and local anaesthetics *vs* local anaesthetics alone in children undergoing surgery

Outcome	Number of trials	Children	RR	95% CI	*P*-value
PONV	11	492	1.25	0.80–1.94	0.33
Bradycardia	8	353	0.33	0.01–7.81	0.49
Hypotension	8	353	—	—	—
Hallucination	7	252	6.0	0.75–47.71	0.09
Sedation	7	290	5.0	0.26–97.70	0.29
Respiratory depression	7	313	—	—	—
Delayed motor function	11	435	0.62	0.19–1.99	0.42
Delayed micturition	7	285	0.72	0.28–1.88	0.50
Nystagmus	2	76	3.00	0.33–27.63	0.33
Neurological complications	5	235	—	—	—

Number of patients requiring rescue analgesia

Five trials[20 21 24 25 27] reported the number of patients requiring rescue analgesia in the postoperative period (24 h). There was a lower RR for rescue analgesia in children receiving a caudal with ketamine in addition to local anaesthetics (RR: 0.71; 95% CI: 0.44–1.15; *P*=0.16).

Duration of motor block (h)

Only two trials[20 21] assessed the duration of a motor block defined as 'time to first spontaneous leg movement' and demonstrated a minor effect on motor impairment after combined local anaesthetic and ketamine (MD: −0.5 h; 95% CI: −5.78–4.78; *P*=0.85).

Time to micturition (h)

The time to micturition was reported in three trials[20 21 28] investigating 112 children. The MD for first spontaneous micturition after surgery was slightly lower in the group receiving a single dose of 0.5[20 21] or 0.25 mg kg^{-1} [28] ketamine combined with 1.75,[20] 2.0,[28] or 2.5 mg kg^{-1} [21] of local anaesthetic (MD: −0.24 h; 95% CI: −0.88 to 0.39; *P*=0.45) compared with local anaesthetic alone.

Adverse events

All 13 trials reported a number of children with various adverse events after caudal regional anaesthesia (Table 5). The most common adverse event was PONV (Fig. 4). Eleven trials with 512 patients[18–20 22 23–26 28 29 30] reported a higher RR of PONV in children receiving 0.25–0.5 mg kg^{-1} ketamine in addition to a local anaesthetic. Bradycardia was assessed by eight trials[18–20 22 24 25 29] and occurred only in one patient receiving 1.5 mg kg^{-1} ropivacaine alone.[18] Eight trials[18–20 22 23–25 29] with 373 children reported no cases of intraoperative hypotension. There was a higher RR of 6.0 (95% CI: 0.75–47.71; *P*=0.09) reported in two[23 26] out of seven trials[18–20 23 26–28] for postoperative hallucination after administration of 0.5 mg kg^{-1} ketamine in addition to a local anaesthetic; the RR for sedation (451 children) reported in one[22] out of seven trials[18 19 21 22 24 27 28] was lower in the treatment group (RR: 5.0; 95% CI: 0.26–97.70; *P*=0.29). Respiratory depression, defined as saturation <95%, was not reported in any of the seven trials[18–20 22 23 25 26] analysing this adverse event. Delayed motor function was analysed in 11 trials[18–20 22 23–25 27 28 29] and a lower RR of 0.62 (95% CI: 0.19–1.99; *P*=0.42) for delayed motor function was observed in the group of patients receiving a local
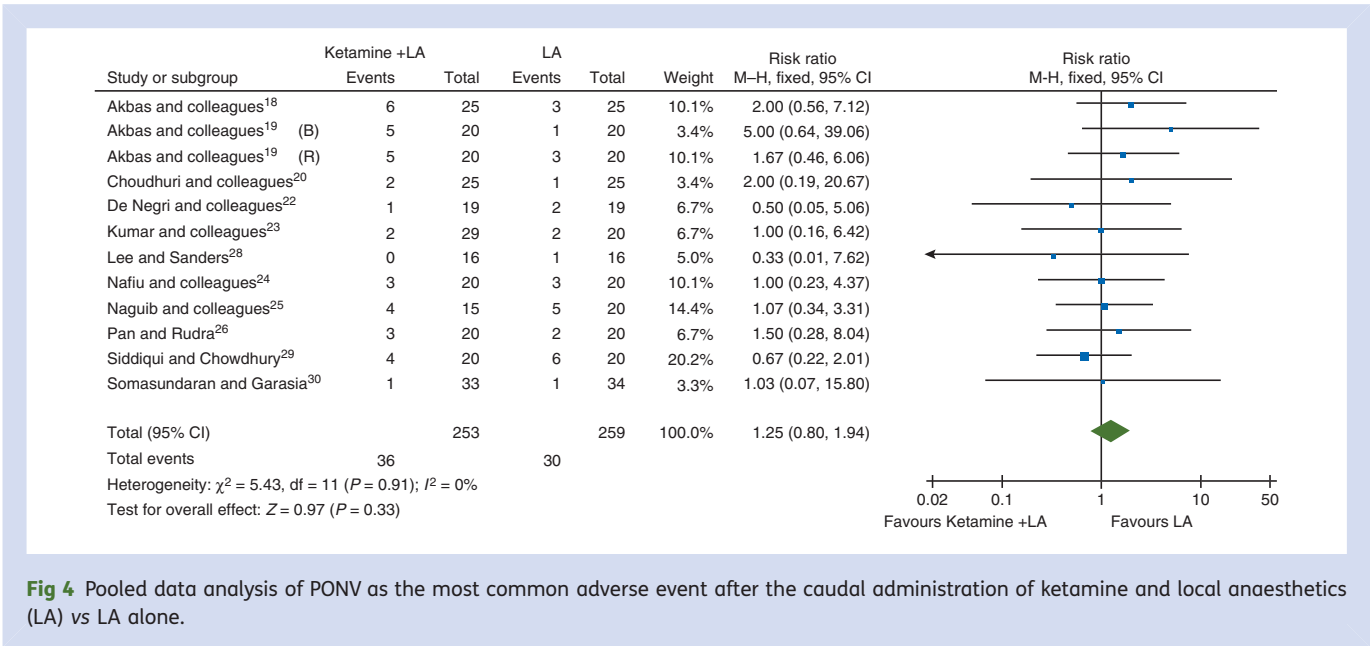
Study or subgroup	Ketamine +LA Events	Total	LA Events	Total	Weight	Risk ratio M–H, fixed, 95% CI	Risk ratio M-H, fixed, 95% CI
Akbas and colleagues[18]	6	25	3	25	10.1%	2.00 (0.56, 7.12)	
Akbas and colleagues[19] (B)	5	20	1	20	3.4%	5.00 (0.64, 39.06)	
Akbas and colleagues[19] (R)	5	20	3	20	10.1%	1.67 (0.46, 6.06)	
Choudhuri and colleagues[20]	2	25	1	25	3.4%	2.00 (0.19, 20.67)	
De Negri and colleagues[22]	1	19	2	19	6.7%	0.50 (0.05, 5.06)	
Kumar and colleagues[23]	2	29	2	20	6.7%	1.00 (0.16, 6.42)	
Lee and Sanders[28]	0	16	1	16	5.0%	0.33 (0.01, 7.62)	
Nafiu and colleagues[24]	3	20	3	20	10.1%	1.00 (0.23, 4.37)	
Naguib and colleagues[25]	4	15	5	20	14.4%	1.07 (0.34, 3.31)	
Pan and Rudra[26]	3	20	2	20	6.7%	1.50 (0.28, 8.04)	
Siddiqui and Chowdhury[29]	4	20	6	20	20.2%	0.67 (0.22, 2.01)	
Somasundaran and Garasia[30]	1	33	1	34	3.3%	1.03 (0.07, 15.80)	
Total (95% CI)		253		259	100.0%	1.25 (0.80, 1.94)	
Total events	36		30				

Heterogeneity: $\chi^2 = 5.43$, df = 11 ($P = 0.91$); $I^2 = 0\%$
Test for overall effect: $Z = 0.97$ ($P = 0.33$)

0.02 0.1 1 10 50
Favours Ketamine +LA Favours LA

Fig 4 Pooled data analysis of PONV as the most common adverse event after the caudal administration of ketamine and local anaesthetics (LA) *vs* LA alone.

anaesthetic combined with 0.5 mg kg^{-1} ketamine. However, trials reporting delayed motor function used higher doses of local anaesthetics in the control group: 1.25,[24] 2.5 mg kg^{-1} bupivacaine.[25 29] Similarly, the RR for delayed micturition (RR: 0.72; 95% CI: 0.28–1.88; $P=0.50$) was lower in the treatment group compared with local anaesthetic alone; again several included studies[24 25 29] used higher doses in the control group compared with the treatment group.[19 22 24–26 28 29] Nystagmus was the most common neurological adverse event and was observed in two trials,[22 29] but more severe neurological complications were not reported. No persistent neurological adverse events were reported in four trials (90 children) which included a neurological follow-up after 6[18 19] or 8 weeks after surgery.[20 23] However, only one trial[20] described the neurological postoperative assessment in detail.

Discussion

Our quantitative systematic review of 13 RCTs including a total of 584 children assessed the efficacy and side-effects of caudal block using local anaesthetic and ketamine in children. The combination provided an extended pain-free interval after operation without the need for rescue medication, a significantly lower use of rescue medication and a low incidence of minor complications in comparison with children receiving only local anaesthetic.

Surveys in different European countries have demonstrated that poor postoperative pain treatment in paediatrics is still a problem.[31 32] Although single-shot caudal epidural anaesthesia is an effective and easy to learn regional analgesia technique in children, the major limitations are a short duration of action (about 4–8 h) and an unwanted motor block after long-lasting local anaesthetics.[6] Several additives including clonidine and ketamine have been investigated to improve analgesic efficacy and reduce local anaesthetic

dose. In a recent survey of paediatric caudal anaesthesia practice in the UK and Ireland, an increased use of ketamine from 32% (2002)[2] to 37.5% (2009)[7] was reported. In contrast, the use of neuraxial ketamine for paediatric anaesthesia in Germany and Switzerland was not recommended[33] due to an ongoing discussion about a potential neurotoxicity of ketamine observed after repeated intrathecal ketamine in rats, mice, and rabbits.[10 34 35]

Our meta-analysis found that the addition of 0.25–0.5 mg kg^{-1} ketamine extended the time to first rescue medication by about 5 h, irrespective of local anaesthetic dose. Thus, the addition of ketamine may reduce the dose requirement of local anaesthetics. There was also a need for rescue analgesia in children receiving ketamine in addition to local anaesthesia, and a qualitative data analysis showed significantly lower rescue analgesic requirements in children receiving additional ketamine. Caudal ketamine is beneficial in increasing the analgesic effect of local anaesthetic analgesia in children, but for some types of surgery, other regional analgesic techniques, such as a dorsal penile block, may offer comparable analgesic properties.[36 37]

Neurological adverse events after caudal ketamine

There has been an ongoing discussion[38] regarding the potential neurotoxicity of caudal ketamine in children.[10 35 39 40] There is some evidence that preservatives like chlorobutanol or benzethonium chloride are responsible for histopathological lesions in the spinal cord, but neuroapoptosis was not investigated.[40–43] Preservative-free ketamine may overcome this concern. However, there is still conflicting experimental evidence from several animal studies regarding intrinsic neurodegeneration of the developing spinal cord after intrathecal preservative-free ketamine. There is an active discussion of how to translate these data to human experience and the applicability of animal studies. Intrathecal administration

of preservative-free ketamine caused a significant neurode-generation of the spinal cord in pups 3 days old (P3), but not in P7 and P21 rats, suggesting that the proapoptotic effect of ketamine is age dependent and occurs at an earlier developmental stage in the spinal cord than in the cortex.[44 45] In terms of neurobiological development of the spinal cord, a P3 rat approximates to a preterm human neonate, P7 rat with a neonate or infant, and P21–P35 rat with adolescent or young adulthood, respectively (www .translatingtime.net).[46–48] In our meta-analysis, caudal keta-mine was given to children aged from 1 month to 12 yr, but no major neuropathological events were observed in the early postoperative follow-up (6–8 weeks after surgery) of four trials.[18–20 23] There are currently no case reports about neurological impairment after single-shot ketamine as an additive in caudal regional anaesthesia. Case reports describing a long-term treatment of chronic cancer pain with neuraxial ketamine have reported variable results about spinal cord degeneration and are influenced by several confounding variables including radiotherapy and chemotherapy that may also be responsible for spinal cord neuroapoptosis.[49–52] To further complicate the picture, there is increasing evidence that systemically administered ketamine has a neuroprotective effect for the brain and spinal cord in children.[53] Our analysis and the conflicting data about neurotoxicity should encourage further safety studies and long-term epidemiological studies of children receiving caudal ketamine.[35 53]

Non-neurological adverse effects

We could not provide an appropriate risk–benefit analysis due to a lack of clinical relevant data, but this is a comprehensive summary of non-neurological adverse events after caudal administration of ketamine. The most common adverse event in those receiving ketamine was PONV, but the influence of PONV prophylaxis was not investigated, as recommended in the current SAMBA guideline.[54] There was a lower RR for extended motor impairment and urinary retention, most likely a result of the reduced dose of local anaesthetic. Sedation and hallucination occurred only rarely in children receiving caudal ketamine and no case of respiratory desaturation, bradycardia, or perioperative hypotension was observed. Except for two children with temporary postoperative nystagmus, there were no reports of major neurotoxic complications in 125 children followed up at 6 or 8 weeks after surgery.

The limitations of our analysis are mainly related to the methodological heterogeneity of several studies. First, the type and dose of local anaesthetic varied between the studies and may have influenced the postoperative analgesic effects and adverse events. However, bupivacaine and ropivacaine are comparably effective in the doses used in the trials included.[55] Secondly, the method of postoperative pain assessment and the different triggers for rescue analgesics may bias the results of our meta-analysis, particularly for duration of analgesia. A consistent standard for pain

assessment in children for investigating paediatric post-operative pain therapy is required. However, most of the pain scales were based on a 10-point scale rating 3 or 4 as pain trigger (Table 2). Thirdly, 11 trials investigated outpatients with postoperative pain assessment and administration of analgesics for pain treatment was mainly performed by parents, which may have influenced postoperative rescue analgesic requirements and postoperative complications but reflects the clinical routine. Fourthly, it is not clear from the methodology of most studies included, if children receiving no rescue analgesia within the 24 h time period were included in the analysis. However, this limitation probably affects both groups equally. Finally, the influence of publication bias cannot be excluded.

Our meta-analysis indicates that adding ketamine to caudal local anaesthetics provides a prolonged and improved postoperative analgesia with few adverse effects compared with local anaesthetics alone. Conflicting preclinical data, which come mainly from rodent studies using repeated intrathecal ketamine injections, about the neurotoxicity of ketamine hinder caudal ketamine from routine use in children. Although no major neurological complications after a single dose of 0.25–0.5 mg kg^{-1} ketamine were observed in the studies in our meta-analysis, preclinical safety studies and larger long-term epidemiological trials investigating possible neurological complications after caudal ketamine administration are warranted.

Conflict of interest

None declared.

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