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① Title- Sub-anesthetic intravenous ketamine vs. caudal bupivacaine for postoperative analgesia in children undergoing infra-umbilical surgeries: a non-inferiority randomized single-blind controlled trial

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③ Running title. iv ketamine vs. caudal bupivacaine

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Sub-anesthetic intravenous ketamine vs. caudal bupivacaine for postoperative analgesia in children undergoing infra-umbilical surgeries: a non-inferiority randomized single-blind controlled trial

Running title: IV ketamine vs. caudal bupivacaine
Abstract

Background: Sub-anesthetic iv ketamine acts as an analgesic and has opioid-sparing effects, particularly for acute postoperative pain. Primary aim of this study was to evaluate the non-inferiority of sub-anesthetic iv ketamine vs caudal bupivacaine for postoperative analgesia in children.

Methods: Children below six years were enrolled in this single-blind study and randomized to receive either sub-anesthetic iv ketamine (0.3 mg/kg) or 1 ml/kg of caudal 0.125% bupivacaine, along with general anesthesia. Postoperative pain was assessed with the FLACC scale at 30 minutes, and at one, two, three, and six hours. Intra and postoperative opioid consumption, time to extubation, postoperative vomiting (POV), postoperative agitation, sedation, and inflammatory markers (serum IL-6 and TNF-α) were also assessed.

Results: One hundred and forty-one children completed the study, 71 in the ketamine and 70 in the caudal group. The cumulative proportion of children without significant postoperative pain (FLACC score < 4) until six hours post-surgery was 45.1% in the ketamine group vs 72.9% in the caudal group (P < 0.001). More children required an additional dose of intraoperative fentanyl (33.8% vs 5.7%; P < 0.001) and postoperative tramadol (54.9% vs. 27.1%; P < 0.001) in the ketamine group. Postoperative agitation, (4.3% vs. 9.9%; P = 0.19) and sedation (32.8% vs 22.5%; P = 0.17) were similar in the groups. Time to extubation, POV, baseline and post-surgical inflammatory markers were comparable.

Conclusions: Sub-anesthetic ketamine is inferior to caudal bupivacaine for postoperative analgesia in children below six years undergoing infra-umbilical surgeries but results in similar postoperative outcomes.

Keywords: Caudal anesthesia; Ketamine; Pediatric; Sub-anesthetic.
Introduction

Caudal epidurals are commonly performed for postoperative pain management in children undergoing abdominal and lower limb surgeries [1,2]. However, apart from procedural failure, there is the possibility of inadvertent dural puncture, infection, and local anesthetic systemic toxicity. Moreover, in children with coagulopathy, pilonidal cyst, spinal dysraphism, or local site infection, caudals are contraindicated [2,3]. Caudal epidurals are also not preferred in some surgeries like hypospadias repair as this causes penile vasodilation, which increases blood loss and may result in fistula formation [4].

Numerous clinical studies support the role of sub-anesthetic iv ketamine as an analgesic, particularly for acute pain in the perioperative setting [5]. Ketamine has been added to local anesthetics in caudal epidurals to prolong postoperative analgesia in pediatric patients, but this still does not eliminate procedural risk, and concerns have also been raised that additives in the epidural or intrathecal space may cause neurotoxicity [5]. A previous study found comparable efficacy of caudal ketamine with caudal bupivacaine for postoperative analgesia in children with better postoperative recovery profiles in the caudal ketamine group [6]. Whether iv sub-anesthetic ketamine provides similar levels of postoperative analgesia as compared to caudal bupivacaine in children is unknown.

Hence, we hypothesized that the analgesic effect of sub-anesthetic iv ketamine is non-inferior to caudal epidural with bupivacaine in children undergoing infra-umbilical surgeries. If proven, this may thus provide an easier option for postoperative analgesia in children without increasing the risk of complications associated with caudal epidurals. In addition, it may obviate the need for multi-modal analgesia and polypharmacy such as non-opioid and opioid analgesics in children who are unable to receive caudal epidurals [7]. The primary aim of this study was to evaluate the efficacy of sub-anesthetic single shot iv ketamine 0.3 mg/kg vs. 1 ml/kg of caudal 0.125% bupivacaine for
postoperative analgesia. Secondary aims were to evaluate the differences in intra and postoperative opioid consumption, and safety of ketamine vs caudal bupivacaine i.e., time to extubation, postoperative vomiting (POV), emergence agitation, sedation, and baseline and post-surgical inflammatory markers between the two groups.
Materials and Methods

Study design

The study was a prospective, single-blind, non-inferiority randomized controlled trial. Children below six years, ASA-PS I&II, posted for elective, infra-umbilical, inguinoscrotal, or lower limb surgeries were enrolled. Exclusion criteria were children with contraindications to caudal anesthesia; cardiovascular diseases; known drug allergy to either ketamine or bupivacaine; children with clotting disorders; or those whose parents/guardians refused to provide consent.

Study approval and trial registration

The Institutional Ethics Committee approved the study (T/IM-F/17-18/16; Chairman: Dr. Suresh Chandra Dash; date of approval 09/01/2018), and written informed consent was obtained from the parent/guardian of each participant. The study was registered prospectively in the Clinical Trials Registry of India (CTRI) (trial registration number: CTRI/2018/02/011822; Principal Investigator; Dr. Alok Kumar Sahoo; study start date 01/03/2018).

Randomization and allocation concealment

Children were randomized into two groups by computer-generated randomization codes. Allocation concealment was with opaque sealed envelopes, which were opened by the attending anesthesiologists, once the patients were received in the preoperative holding area on the day of the surgery. Because a sham caudal group was not planned, the anesthesiologists were aware of group allocation.
**Anesthesia protocol**

Monitoring, anesthesia, fluid, and temperature management were standardized in both groups. Children with prior iv line were given iv midazolam 0.1 mg/kg, 5 minutes before parental separation, and children without an iv line were given oral midazolam 0.5 mg/kg, 30 minutes before parental separation.

Induction of anesthesia was carried out with inj. glycopyrrolate 10 μg/kg, fentanyl 2 μg/kg and propofol 2 mg/kg. Muscle relaxation was achieved with inj. atracurium 0.5 mg/kg. The airway was secured with the appropriate size of tracheal tubes or supraglottic airway devices. Anesthesia was maintained with a mixture of oxygen in air, and sevoflurane at one MAC. After induction, 2–3 ml of blood was collected for measuring IL-6 and TNF-α levels (baseline) since both cytokines are markers of inflammation and associated with pro-nociceptive activity.

Following induction of anesthesia, children randomized to the ketamine group received a sub-anesthetic dose of iv ketamine (0.3 mg/kg), and those randomized to the caudal group were given caudal epidural using loss of resistance technique with 1 ml/kg of 0.125% bupivacaine with a maximum dose of 2 mg/kg. Inj. fentanyl (0.25 μg/kg) was supplemented if the heart rate and/or blood pressure responses were > 20% from baseline. Apart from this, all children received 15 mg/kg of iv acetaminophen at induction and continued 8th hourly for the first 24 hours.

Antagonism of neuromuscular blockade was carried out with inj. glycopyrrolate 10 μg/kg and neostigmine 50 μg/kg. The time to extubation after antagonism of the neuromuscular blockade was also noted. The incidence of emergence agitation measured with the Watcha scale was noted in the first 30 minutes of antagonism of neuromuscular blockade. A score of ≥ 2 was considered positive for emergence agitation [8]. A second blood sample was drawn three hours post-surgery to determine the level of the inflammatory markers.
In the postoperative anesthesia care unit (PACU), the pain was assessed with the faces, legs, arm, cry and consolability (FLACC) scale at 30 minutes, one and two hours, and subsequently at three and six hours in the surgical ward [9]. The license to use the FLACC scale was taken from the University of Michigan Office of Technology (License Agreement #9709-umich). Children having FLACC score ≥ 4 at any point of time within six hours were considered as having a positive pain response. Children having a positive pain response were given iv rescue analgesia with inj. tramadol 1 mg/kg.

Ramsay sedation score (RSS) was used to assess the sedation in the PACU. RSS > 3 signified excessive sedation. Another adverse effect considered was POV. All postoperative outcome assessments were carried out by trained nursing personnel who were blinded to the groups. The study period was from induction of anesthesia to six hours postoperative.

**Primary aim and outcome parameter**

The primary aim was to evaluate the non-inferiority of sub-anesthetic ketamine (0.3 mg/kg) vs.1 ml/kg of 0.125%-caudal bupivacaine for postoperative pain. The outcome parameter assessed for the primary aim was the cumulative proportion of children with FLACC score ≥ 4 at the end of six hours.

**Secondary aims**

Secondary aims were to evaluate the differences in intra and postoperative opioid requirements and safety of ketamine vs caudal bupivacaine i.e., time to extubation following neuromuscular block antagonism, POV, postoperative agitation, sedation, and baseline and post-surgical inflammation.

**Statistics**

A sample size of 72 was required in each group to prove non-inferiority whose margin was set at 5% beyond which it was considered not be clinically meaningful. The caudal analgesia group’s
response rate (i.e., the proportion of children with FLACC score \( \leq 4 \) at 6 hours) was set at 96% [10], and the iv ketamine group’s response rate was set at 90%, considering this will be clinically significant for pain relief. The sample size was powered to 80%, allowing an alpha error of 0.05. A drop out of 10% was considered for sample size calculation.

The Shapiro-Wilk test was used to assess the normality of the data. Parametric data were analyzed by the unpaired t-test. Non-parametric data were analyzed by the Mann-Whitney U test. Categorical data were analyzed by the Chi-square test. Regression techniques were used to determine the association between variables. P value <0.05 (2-tailed) was considered significant. Data were analyzed by R software (Version 3.5, R studio, Geneva).
Results

A total of 159 children were considered over one and a half years, of which 141 completed the study, 71 in the ketamine group and 70 in the caudal group (Fig. 1, CONSORT diagram). We excluded two children in the caudal group due to a change in surgical plan and one in the ketamine group due to data collection failure.

Baseline characteristics like age, sex, and weight were comparable in both groups (Table 1). Surgeries were mostly short duration (≤ 90 minutes) and similar in both groups. Different infraumbilical surgeries included in the study were inguinal hernia repairs, hypospadias & chordae correction, undescended testis correction, surgery of ureter and urethra (non-hypospadias), bladder procedures and various other surgeries (Table 1).

Primary outcome

The proportion of children having FLACC score < 4 at the end of six hours post-surgery was 45.1% in the ketamine group compared to 72.9% in the caudal group (p < 0.001) (Fig. 2, Table 2). The mean FLACC score in caudal group was significantly lower at 30 min, 1, 2 and 3 hour (p < 0.001) (Fig 3). The lower limit of the confidence interval (–0.47) for the difference in response rates at six hours in terms of the FLACC score < 4 between ketamine and caudal groups crossed the non-inferiority limit of - 0.05, showing that sub-anesthetic iv ketamine was inferior to caudal analgesia. Mixed effect modeling of the FLACC response at various time points with groups as covariant, showed a significant difference in the two groups' response trend across all the time points (P < 0.05).

Secondary outcome

Thirty-three percent of children required an additional dose of intraoperative fentanyl in the sub-anesthetic ketamine group in comparison to 5.7% in the caudal epidural group (P < 0.001). The mean dose of fentanyl also significantly higher in Ketamine group (Table 2). The standardized mean
difference between two groups for fentanyl consumption was 0.56. The proportion of children requiring postoperative tramadol were also significantly more in the sub-anesthetic ketamine group in the first six postoperative hours (54.9% vs. 27.1%; P < 0.001) (Table 2).

The time to tracheal extubation was comparable in both groups (Table 2). Postoperative agitation and sedation were similar in both groups (Table 2). Only four children, three in the ketamine and one in the caudal group had POV in this study. Serum TNF-α and IL-6 levels were less in ketamine group in comparison to caudal group though the difference was not statistically significant at the postoperative time points (Table 2).
Discussion

This study's main finding was that sub-anesthetic ketamine was inferior to caudal epidural analgesia with bupivacaine for postoperative pain relief measured with FLACC score till six hours in children undergoing infra-umbilical surgeries under general anesthesia. The FLACC score at the sixth postoperative hour was similar in both the groups possibly due to the wearing of the caudal effect. However, the degree of early postoperative inflammation and other secondary outcomes like POV, sedation, and emergence agitation were similar in both groups.

Ketamine causes spinal inhibition of nociceptive transmission [11]. Sub-anesthetic ketamine has been widely used for postoperative pain relief, but controversy still exists regarding the optimal dose, duration, and administration timing [12, 13]. Our results are different from those of Naguib and colleagues [6]. In a study in 50 children, they found comparable analgesic efficacy of low-dose caudal ketamine (0.5 mg/kg) with 1 ml/kg of caudal 0.25% bupivacaine. In their study, the analgesic efficacy of caudal ketamine was seen till 24 hours postoperatively. Significantly a greater number of children in the caudal ketamine group in their study were calm and cheerful postoperatively at 60 and 90 minutes compared to the caudal bupivacaine group. Differences in our study vs. Naguib’s could have been due to the route of administration and the dose of ketamine (0.3 mg/kg in our study vs. 0.5 mg/kg in Naguib’s). Again, a lack of difference in postoperative recovery profiles in our study could be similarly explained by the difference in the pharmacodynamics of the iv vs epidural route. Thus, the equivalence of the two routes for ketamine probably does not exist.

Our study has similar findings as Dix and colleagues, wherein 75 children were given either iv pre-incisional bolus (0.5 mg/kg) or pre-incisional bolus (0.5 mg/kg) followed by postoperative infusion (4 µg/kg/min) of ketamine vs saline placebo during appendicectomy [14]. They did not find any improvement in pain score (at rest or on movement) or decrease in morphine consumption in the ketamine groups. They concluded that ketamine might not have the same opioid-sparing effect in
children as is seen in adults [14]. Another lack of effect in our study could be that patients received pre-emptive ketamine. It has been shown that ketamine may block the NMDA receptors more effectively in adults if it has been opened by intense or noxious stimuli or the so-called ‘foot in the door blockade’ phenomenon [15]. A similar phenomenon may be possible in pediatric patients. Thus, the timing of administration, i.e. pre-emptive vs post-surgical may lead to different responses.

IL-6 and TNF-α are major proinflammatory acute-phase proteins secreted in response to tissue damage caused by surgery. These cytokines have been known to modulate inflammation, nociception and possibly contribute to intensifying pain experiences. Increased levels of these cytokines are associated with greater inflammation and pain [16]. Previous studies have shown that ketamine has anti-inflammatory effects and it reduces the pro-inflammatory cytokines TNF-α and IL6 by immunomodulation [17-20]. This regulatory action was more pronounced when ketamine was administered before the noxious stimulus. In our study, similar cytokine levels post-surgery between the ketamine and caudal groups suggests that even though ketamine was inferior to caudal bupivacaine for postoperative analgesia, the anti-inflammatory response was similar. The three-hour postoperative window period for the sampling of the postoperative inflammatory markers were in-line with previous studies, since TNF-α decays by the 3rd hour after exposure to toxins/surgery, while IL-6 levels are detected in blood by the second hour and peaks at 12-24 hours post surgery [21,22]. We are unable to comment on the apparent dissociation of the inflammatory and nociceptive action, but it is possible that a peak effect may have been missed in the two groups due to the difference in the time of rise of both the markers.

The adverse effects were comparable, showing the safety of iv sub-anesthetic ketamine. Ketamine can cause excessive sedation and agitation; however, the effect is more pronounced with anesthetic dose [23]. In our patients, we found the extubation time, sedation, and emergence agitation scores
were similar in both groups. Our findings are similar to the findings of Sinha and colleagues [24], where they found that caudal ketamine does not increase agitation and emergence. Thus, sub-anesthetic ketamine has a good safety profile in this cohort of patients.

The main limitation of our study was the absence of a placebo group, but then, our aim was not to show the superiority of ketamine vs. placebo for postoperative analgesia; rather, the non-inferiority of the intervention with caudal epidurals to test the hypothesis whether it could replace the “kiddie” caudal. Second, we followed patients for six hours post-surgery. However, the FLACC response until six hours was considered in this study, as the effects of even “kiddie” caudals wear off in a sizeable proportion of children after this time [25]. The action of a bolus dose of subanesthetic ketamine is unlikely to last for a long duration and this is also a potential limitation of the study. However, in children, there is very limited evidence on postsurgical administration of subanesthetic ketamine, and thus, we are unable to comment on whether the timing of administration of ketamine would be more appropriate after surgery in this cohort of patients. Another limitation was that some of the outcomes like intraoperative opioids and time to extubation were not blinded.

In conclusion, a sub-anesthetic dose of iv ketamine is inferior to caudal analgesia with bupivacaine in children below six years undergoing infra-umbilical surgeries. Unless there is no specific contraindication, children in this age group should continue to receive caudal epidurals for postoperative analgesia for this spectrum of surgeries. Further studies can be designed to study the effect of infusions of ketamine or even post-surgery sub-anesthetic administration.
References


19. Chen MH, Li CT, Lin WC, Hong CJ, Tu PC, Bai YM, et al. Rapid inflammation modulation and antidepressant efficacy of a low-dose ketamine infusion in treatment-


Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Caudal group</th>
<th>Ketamine group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>39.7 ± 22.4</td>
<td>41.4 ± 22.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>13.4 ± 5.2</td>
<td>14.2 ± 5</td>
<td>0.4</td>
</tr>
<tr>
<td>Sex (M: F)</td>
<td>62 : 8</td>
<td>59 : 12</td>
<td></td>
</tr>
<tr>
<td>Duration of Surgery (min)</td>
<td>95.1 ± 48.8</td>
<td>83.6 ± 50.5</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Types of Surgery

- Inguinal hernia repairs: 19 (25)
- Hypospadias & chordae correction: 17 (14)
- Undescended testis: 10 (11)
- Others: 24 (21)

Values are mean ± SD or number of patients
Table 2. Primary and Secondary Outcome Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Caudal group (n = 70)</th>
<th>Ketamine group (n = 71)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLACC &lt; 4, till 6-hr (Cumulative)</td>
<td>51 (72.9%)</td>
<td>32 (45.1%)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Time to extubation (minutes)</td>
<td>7.3 ± 3.5</td>
<td>7.2 ± 2.8</td>
<td>-1.2 to 0.9</td>
<td>0.75</td>
</tr>
<tr>
<td>Additional Fentanyl (intraoperative)</td>
<td>4 (5.7%)</td>
<td>24 (33.8%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Additional dose of Fentanyl (µg/kg) (intraoperative)</td>
<td>1.0 ± 3.4</td>
<td>3.7 ± 5.8</td>
<td>1.1 to 4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additional Tramadol (postoperative)</td>
<td>19 (27.1%)</td>
<td>39 (54.9%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Preop TNF-α (µg/ml)</td>
<td>17.4 ± 12.2</td>
<td>15.8 ± 11.6</td>
<td>-2.9 to 6.03</td>
<td>0.5</td>
</tr>
<tr>
<td>Postop 3-hr TNF-α (µg/ml)</td>
<td>25.4 ± 18.7</td>
<td>21.9 ± 16.1</td>
<td>-3.1 to 10.04</td>
<td>0.3</td>
</tr>
<tr>
<td>RSS</td>
<td>23 (32.8%)</td>
<td>16 (22.5%)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Sedation (&gt; 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergence Agitation</td>
<td>3 (4.3%)</td>
<td>7 (9.9%)</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD or number of patients (%). FLACC- Face, Legs, Activity, Cry, Consolability scale; RSS- Ramsay Sedation Scale.
Figure legends

**CONSORT Flow Diagram**

![Flow Diagram](image)

**Fig. 1.** CONSORT flow Diagram.
Fig. 2. Cumulative 6-hr postoperative FLACC Score between the groups.
**Fig 3** - Mean FLACC Score between the groups over the time

* P < 0.001