Original Article

Topical versus caudal ketamine/bupivacaine combination for postoperative analgesia in children undergoing inguinal herniotomy

ABSTRACT

Background: Multiple studies claim that caudal administration of ketamine causes effective postoperative analgesia. The aim of this study was to assess the clinical effectiveness of ketamine after caudal or topical administration in pediatric patients undergoing inguinal herniotomy.

Patients and Methods: This randomized, comparative, double-blind study included eighty children (aged 6 months to 6 years) received either 1 ml/kg of 0.25% bupivacaine/ketamine 0.5 mg/kg for caudal analgesia (caudal group) or 0.3 ml/kg of 0.25% bupivacaine/ketamine 0.5 mg/kg sprayed by the surgeon around the spermatic cord and upon the ilioinguinal nerve before wound closure for topical analgesia (topical group). The duration of postoperative analgesia, pain scores, rescue analgesic consumption, sedation score, hemodynamic monitoring, and side-effects were evaluated 48 h postoperative.

Results: Kaplan–Meier survival analysis of analgesia free time demonstrated a significant advantage of topical ketamine (TK) group over caudal ketamine (CK) group. The duration of postoperative analgesia was longer in TK group than in CK group (28.74 ± 2.88 vs. 21.43 ± 5.01 h, $P = 0.000$). Fewer children asked for oral analgesics in the topical group (24 of 36, 66.7%) than in the caudal one (28 of 32, 87.5%; $P < 0.01$). Postoperative pain scores at the 6th till 48th h were lower in topical group with comparable analgesic consumption between two groups. In the caudal group, four subjects suffered from retention of urine: Two presented with a residual motor block and two had photophobia.

Conclusion: Wound instillation of bupivacaine/ketamine is a simple, noninvasive, and effective technique that could be a safe alternative to CK for postoperative analgesia in children undergoing inguinal hernia repair.

Key words: Analgesia; caudal; day-case anesthetic techniques; ketamine; pediatrics; postoperative; topical

Introduction

Caudal analgesia along with general anesthesia is a very popular regional technique for prolonged postoperative analgesia in different pediatric surgical procedures where the surgical site is subumbilical. Caudal anesthetics usually provide analgesia for approximately 4–6 h.[1]

Ketamine added to bupivacaine in caudal block (CB) was shown to increase the duration of postoperative analgesia.[2] The analgesic effect of caudal epidural ketamine is probably due to its interaction with the glutamate N-methyl-D-aspartate (NMDA) receptors or opioid receptors in the spinal cord.[3]

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CB involves the introduction of a local anesthetic (LA) into caudal epidural space, requires the child to be positioned appropriately under deep sedation or general anesthesia, needs skill, and is operator dependent. The risk of technical failure exists and the use of sonography improved the precision of CB and increased success rate of caudal injection.[4] It can cause complications such as bone marrow puncture, intestinal damage, infection, hematoma, inadvertent subcutaneous, subarachnoid or intravascular injection of the LA, and systemic toxicity.[5] Other associated adverse effects include urinary retention and possible motor blockade.[6] The central nervous system disorders, spinal deformities, inflammation of the block site, and coagulation disorders are contra-indications for caudal anesthesia, so the search continues to find a less invasive substitute to control pain.

Compared with caudal analgesia, intraoperative wound instillation with an LA is a simple, effective, noninvasive and inexpensive means of providing postoperative analgesia that could offer the advantage of lower costs, time, and risks.[7,8] Topical approaches to analgesia have the potential to produce pain relief with minimal adverse systemic effects due to low plasma levels.[8] NMDA and other glutamate receptors have been found to be located peripherally on sensory afferent nerve endings and on cells adjacent to the nerve endings (e.g., keratinocytes, immune cells).[9,10] This provided the initial impetus for exploring the peripheral and topical applications of ketamine.[11]

The aim of this study was to compare the postoperative analgesic efficacy and adverse effects of low-dose ketamine/bupivacaine combination administered either caudally or topically in children undergoing day-case unilateral inguinal herniotomy.

Patients and Methods

Subjects

This prospective, randomized, double-blind comparative study was approved by the Local Research Ethics Committee, Faculty of Medicine, Assiut University, Egypt, was registered at ClinicalTrials.gov (NCT02462174) and followed Helsinki Declaration. After obtaining written informed consent from parents, we enrolled a total of eighty male subjects aged 6 months to 6 years of the American Society of Anesthesiologists physical Status I or II, undergoing day-case, elective unilateral inguinal herniotomy. Excluded from the study were children with a history of developmental delay or mental retardation, clinically important renal, hepatic, cardiac, or neurological conditions, seizures, known or suspected coagulopathy, allergy to any LA, congenital anomaly of the spine, or infection at the sacral region.

Anesthesia

After standard fasting times and without premedication, anesthesia was induced with 8% of sevoflurane in 100% oxygen. Standard monitoring included electrocardiography, end-tidal carbon dioxide, arterial oxygen saturation continuously, and noninvasive blood pressure every 5 min (Cardiocap II, Datex-Ohmeda, Finland). The airway was established using a laryngeal mask airway (LMA). Anesthesia was maintained with sevoflurane in 50% oxygen/air mixture, and the depth of anesthesia was adjusted accordingly with a goal of 80–120% baseline noninvasive mean arterial pressure. Spontaneous breathing was maintained during surgery. All patients received intravenous (IV) paracetamol 15 mg/kg. No sedatives or opioids were administered during operation. At the end of surgery, the LMA was removed, and the child was transferred to the Post-Anesthetic Care Unit so long as there was no postoperative compromise in the airway or hemodynamic instability. Pain intensity and Aldrete–Krolik recovery score[12] were recorded every 10 min until an Aldrete score >9 was achieved. Thereafter, patients were transferred to the ward.

Intervention

Enrolled children were randomly assigned according to a computer-generated randomization table to two intervention groups (of forty patients each) either:

Caudal ketamine (CK) group patients received 1 ml/kg of 0.25% bupivacaine combined with 0.5 mg/kg ketamine (ketamine HCl, 50 mg/ml, Sigma Tec, Egypt) or

Topical ketamine group (TK) patients received 0.3 ml/kg bupivacaine 0.25% and 0.5 mg/kg ketamine locally installed by the surgeon around the spermatic cord and upon the ilioinguinal nerve before wound closure.

An investigator who did not participate in the care of the enrolled children prepared study medications according to group assignment.

CK group patients were placed in the lateral decubitus position and under sterile conditions, a consultant anesthetist performed a single-shot blind technique CB after induction of anesthesia and before surgery and 1 ml/kg of 0.25% bupivacaine combined with 0.5 mg/kg ketamine was injected (maximum volume = 20 ml). Fifteen minutes after performing CB, surgery was initiated. Cardioacceleration changes (increasing heart rate and noninvasive mean arterial pressure >15% in response to noxious surgical stimulation) and/or patient movement of his limbs were interpreted as insufficient analgesia. In such instances, CB was considered failed, then 1–2 μg/kg IV

fentanyl were administered, and the patient was excluded from the study.

Topical ketamine group patients did not receive any caudal intervention. Otherwise, a mixture of 0.3 ml/kg bupivacaine 0.25% and 0.5 mg/kg ketamine was sprayed by the surgeon around the spermatic cord and upon the ilioinguinal nerve (running medially through the inguinal canal along with cord structures[13]) and adjacent structures in a fan-shaped manner. The study drugs were locally installed at the end of the operative procedure, after identification and ligation of the hernial sac and before skin closure.

Assessments

Health-care personnel providing direct patient care, patients, and their parents were blinded to group allocation.

Intraoperative assessments included; the heart rate, noninvasive blood pressure, and peripheral oxygen saturation recorded before and after induction of general anesthesia, immediately, 10 min, 20 min, and 30 min after skin incision, and at the end of surgery.

Postoperative assessments

Postoperative pain during hospital stay was assessed using the children and infant postoperative pain scale[14] (CHIPPS, 0–10) and the faces legs activity cry consolability scale[15] (FLACC, 0–10) at 0, 15, 30, 60, 120, and 180 min after recovery from anesthesia. IV paracetamol 15 mg/kg was administered for rescue analgesia if two coupled observations separated by a 5 min waiting period yielded both CHIPPS and FLACC ≥4.

Postoperative agitation was evaluated at 0, 15, 30, and 60 min after recovery from anesthesia using a four-point agitation scale (1 = the child is calm, quiet; 2 = crying but can be consoled; 3 = crying, cannot be consoled; and 4 = agitated, restless, and thrashing around).[16] Postoperative agitation was defined as a score of ≥3. Motor block was assessed using a modified Bromage score (0 = no motor block, 1 = able to move legs, and 2 = unable to move legs) at 0, 15, 30, 60, 120, and 180 min postoperative.[17] The significant residual motor blockade was defined as a motor block score ≥1 point. In the event of an asymmetric block, the highest numerical value was recorded.

Perioperative adverse events including bradycardia, hypotension, respiratory depression, fever >38.3°C, retching, vomiting, or urine retention were treated and recorded. The decision to place a urinary catheter for urinary retention and evaluation of micturition were made by a urologist. Children were discharged from hospital 4 h after surgery if they were conscious, hemodynamically stable, pain-free, started oral intake, voiding, walking in an appropriate manner for age, with absence of retching, vomiting, or other side-effects. The parents were actively involved in the clinical trial and were invited to complete a postoperative chart with a numeric rating pain scale (NRS) ranging from 0 to 10 (with zero = no pain and 10 = the worst pain imaginable).[18] The parents were instructed to assess pain at least once an hour and to give their children 10 mg/kg of oral ibuprofen if NRS were ≥3. Information regarding pain levels and the use of analgesia after discharge was obtained through telephone calls to parents at 6, 12, 18, 24, and 48 h after surgery.

At the end of the study, parents were asked to express their overall satisfaction about the analgesic care of their children using a four-point Likert scale (1 = excellent, 2 = good, 3 = fair, and 4 = poor).[19] One week after the operation, the surgical wound was checked to rule out other problems such as wound infection or dehiscence.

Statistical analysis

The primary endpoint of this study was the duration of postoperative analgesia measured by the time to the first request for rescue analgesics. Based on previous studies,[2,8] a target sample size was calculated. A power analysis estimated that a sample size of thirty patients in each group would have an 80% power at 0.05 level of significance to detect a difference of 1 h in the time to the first request for rescue analgesics between the two groups. To compensate for patients drop out, a total of eighty subjects were enrolled.

Distribution of baseline variables was assessed by Shapiro-Wilk tests. Continuous data were reported as a mean ± standard error and were analyzed using two-sample (unpaired) *t*-test or analysis of variance for multiple comparisons with least significant difference test for *post hoc* analysis. Categorical data were reported as percentages and were analyzed using the Chi-square test or Fisher exact test as appropriate. Nonparametric data such as pain scores were reported as median and interquartile range and were analyzed using the Mann–Whitney U-test. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics version 20 (SPSS Inc., Chicago, IL, USA).

Results

Eighty subjects were enrolled in the study and twelve were excluded in total. Four children were excluded because of failure of CB (CK group). Three children (one in CK group and two in TK group) were excluded because they received medications including a nonsteroidal anti-inflammatory drug

during the study period because of an upper respiratory tract infection after discharge. Lastly, we could not contact the parents of another five children (three in CK group and two in TK group). A final of 68 children were subjected to statistical analysis (n = 32 in CK group and n = 36 in TK group [Figure 1]). The two groups did not differ in terms of patient characteristic data and surgical profiles [Table 1]. A longer anesthesia time was observed in CK group (49.63 ± 2.98 vs. 39.82 ± 2.74 min, P = 0.000).

The hemodynamic parameters did not indicate any significant differences over time inside each group or between groups. Compared to the caudal group, the mean agitation scores in topical ketamine group were higher immediately after recovery (P < 0.001), lower at 15 min (P < 0.003) and 30 min (P = 0.000) after recovery and comparable at 60 min postoperative. No child in the study presented with agitation score ≥3 [Table 2]. Residual motor block with modified Bromage score ≥1 was observed in two patients in CK group [Table 3].

Until discharge from the hospital, the mean CHIPPS and FLACC scores were comparable between the two groups (P > 0.05) at all-time points except for CHIPPS scores at 15 min postoperative [Figures 2 and 3], and no patient requested for rescue analgesia in either group. Figure 4 represents NRS pain scores determined by parents from 6 to 48th h postoperative. TK group patients had significantly

Table 1: Patient characteristics and intraoperative data

Item	Group CK (n=32)	Group TK (n=36)	P
Age (years)	2.86±1.73 (0.85-6)	3.07±2.13 (0.45-6)	0.662^{NS}
Weight (kg)	13.01±4.29 (7.50-22)	14.41±5.75 (5-26)	0.270^{NS}
Height (cm)	74.81±17.62 (50-115)	74.79±17.02 (50-110)	0.971^{NS}
ASA I/II	28/4	28/8	0.271
Side of operation (right/left)	24/8	20/16	0.201
Surgery time (min)	35.06±2.95	33.09±3.01	0.209
Anesthesia time (min)	49.63±2.98	39.82±2.74	0.000
Recovery time (min)	3±1.68	2.62±1.01	0.265^{NS}
Hemoglobin (g/dl)	11.12±1.37	10.86±1.37	0.452^{NS}
Platelet (×10^9/L)	371.75±96.62	422.61±126.08	0.072^{NS}
Prothrombin concentration (%)	95.13±6.26	94.18±8.02	0.372
INR	1.05±0.04	1.07±0.12	0.495

Data are represented as a mean±SE and range. ^{NS}Nonsignificant; P<0.05 versus CK group. SE: Standard error; ASA: American Society of Anesthesiologists; INR: International normalized ratio; CK: Caudal ketamine; TK: Topical ketamine

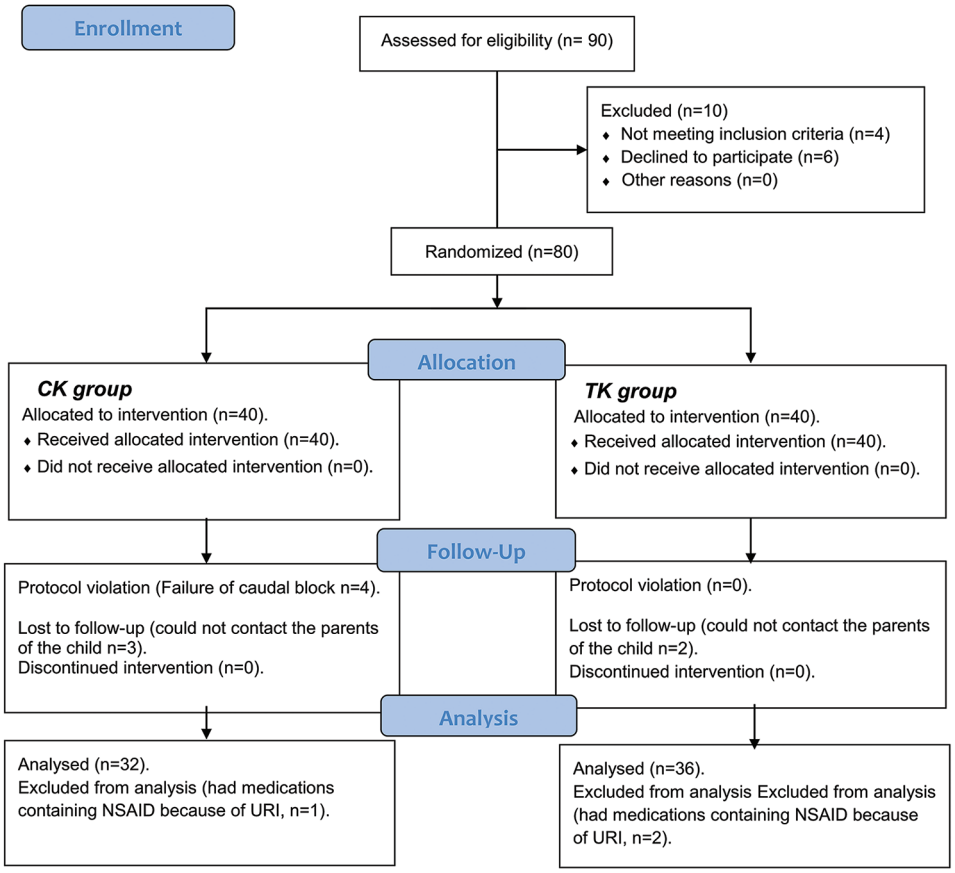

Figure 1: Participant flow diagram. CK: Caudal ketamine, TK: Topical ketamine, NSAID: Nonsteroidal anti-inflammatory drug, URI: Upper respiratory tract infection

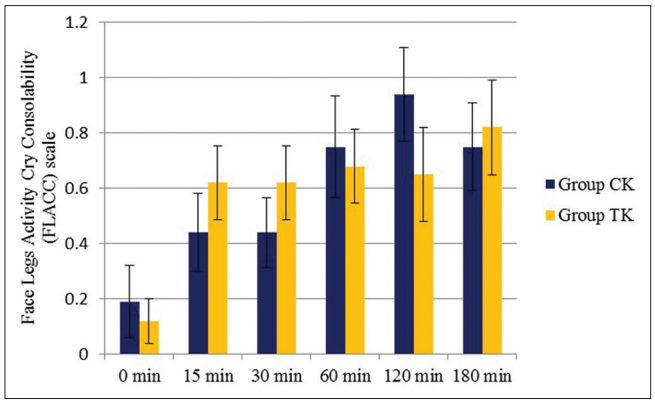

Figure 2: The face legs activity cry consolability scale. Face legs activity cry consolability scores after the surgery were comparable between the two groups at all-time points (*P* > 0.05 vs. group caudal ketamine)

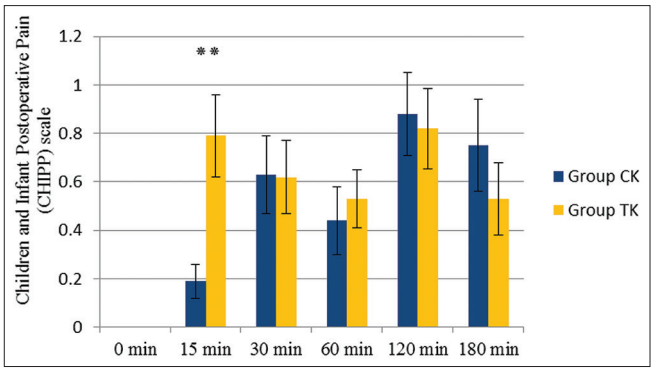

Figure 3: Children and infant postoperative pain scale. Children and infant postoperative pain scores after the surgery were comparable between the two groups at all-time points with the exception of scores at 15 min postoperative (P* < 0.05 vs. group caudal ketamine)**

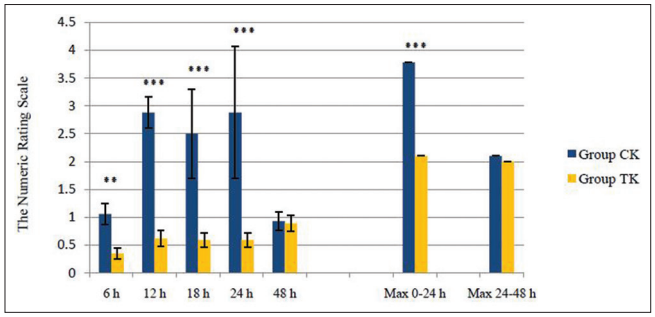

Figure 4: The numeric rating scale. Numeric rating scale scores during the 48 h postoperative period. Maximum 0–24, maximal numeric rating pain scale score during postoperative 0–24 h; maximum 24–48, maximal numeric rating pain scale score during postoperative 24–48 h (P* < 0.05 vs. group caudal ketamine)**

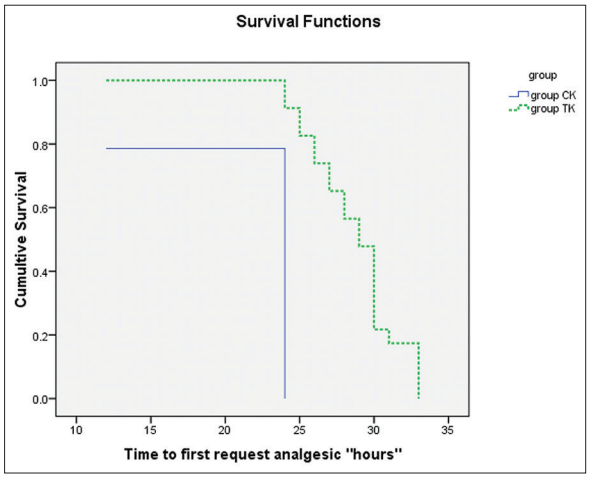

Figure 5: Kaplan–Meier curve for time to first oral analgesic administration. Kaplan–Meier survival analysis of analgesia free time demonstrated a significant advantage of topical ketamine group over caudal ketamine group (log rank *P* = 0.000)

lower NRS scores than CK group at all-time points, except for scores at 48th h postoperative.

During the 48 h observation time, fewer children asked for additional analgesics in topical ketamine group (24 of 36, 66.7%) than in the caudal one (28 of 32, 87.5%; $P = 0.01$). Kaplan–Meier survival analysis of analgesia free time demonstrated a significant advantage of TK group over CK group (log rank $P = 0.000$) [Figure 5]. The mean duration of analgesic effect of techniques used as indicated by the time to administration of first rescue analgesia was longer in topical ketamine group than in CK group (28.74 ± 2.88 vs. 21.43 ± 5.01 h, $P = 0.000$) with no significant difference in postoperative analgesic consumption between the two groups (191.07 ± 90.80 vs. 163.83 ± 114.52 mg, $P = 0.348$; [Table 4]).

Adverse psychological effects or respiratory depression was not seen in either group. No patient in the study developed wound infection or dehiscence. Four children suffered from retention of urine and were catheterized in CK group, and the perioperative adverse events are demonstrated in Table 5.

Table 2: Four-point agitation scale

Item (min)	Group CK (*n*=32)	Group TK (*n*=36)	*P*
0	0.13±0.08	0.56±0.08	0.001
15	0.81±0.07	0.47±0.087	0.003
30	0.88±0.059	0.47±0.087	0.000
60	0.50±0.09	0.44±0.086	0.638^{NS}

Data are represented as a mean±SE. $P<0.05$ versus group CK, ^{NS}Nonsignificant. SE: Standard error; CK: Caudal ketamine; TK: Topical ketamine

Table 3: Modified Bromage scores within the caudal ketamine group (*n*=32)

Time (min)	Modified Bromage score (%)		
	0	1	2
0	24 (75)	2 (6.25)	6 (18.75)
15	26 (81.25)	0 (0)	6 (18.75)
30	28 (87.5)	2 (6.25)	2 (6.25)
60	30 (93.75)	0 (0)	2 (6.25)
120	30 (93.75)	0 (0)	2 (6.25)
180	30 (93.75)	0 (0)	2 (6.25)

Data are represented as numbers and percentages

Finally, a significantly higher family satisfaction scores were recorded in TK group ($P = 0.000$) compared to CK group [Table 6].

Discussion

In this study, we demonstrated that topical ketamine/bupivacaine significantly prolonged the duration of postoperative analgesia. Compared with the caudal route, the topical drug combination also provided lower postoperative NRS scores, reduced number for analgesic requests with no difference in total oral analgesic consumption in the 1st 48 h postoperative.

The key nerves in the inguinal region are the ilioinguinal nerve, iliohypogastric nerve, and genital branch of the genitofemoral nerve.[13] In the current study, we could visualize the ilioinguinal nerve and spray our LA combination under direct vision. The other two nerves are difficult to directly visualize while lying within the spermatic cord. However, with spraying our LA generously along the spermatic cord and adjacent structures, we can suspect that those nerves were also anesthetized.

In the current study, postoperative pain during hospital stay was assessed with two types of pain scales for infants and children (CHIPPS and FLACC scales) to avoid inappropriate administration of IV analgesics. Except for CHIPPS score at 15 min, differences in pain scores were not clinically significant between the two groups for the first 3 h postoperative. Clinically relevant differences in pain scores between the two groups occurred after 12 h after surgery, and this is consistent with the end of analgesic duration of ketamine.[2,20] The difference in early postoperative CHIPPS score at 15 min in the topical group is consistent with the time needed to reach a peak effect, compared with the preemptive caudal route. Postoperative agitation scores in the topical group were higher on recovery from anesthesia and lower from 15 min postoperative afterward, and as pain is an integral component in agitation assessment, this difference also may be attributed to the time needed to reach a peak effect.

The duration of postoperative analgesia in CK group is consistent with previous reports of CK in association with bupivacaine for intra- and post-operative analgesia.[2,20]

Despite the clinical effectiveness of CK/bupivacaine, four children were excluded from analysis because of failure of CB, another four suffered from retention of urine, and two developed residual postoperative motor weakness. The caudal epidural analgesia has two main drawbacks.

Table 4: Consumption of rescue oral analgesic medications in the 1st 48 h postoperative

Item	Group CK ($n=32$)	Group TK ($n=36$)	*P*
Analgesia time (h)	21.43±5.01 (12-24) ($n=28$)	28.74±2.88 (24-33) ($n=24$)	0.000
Patients receiving their 1st pain rescue medications (%)			
0-4th h postoperative	0	0	0.01
4-10th h postoperative	0	0	
10-20th h postoperative	6 (18.75)	0	
20-30th h postoperative	22 (68.75)	12 (33.33)	
30-48th h postoperative	0	12 (33.33)	
Total patient requests for analgesia in the 1st 48 h postoperative (%)			
No request	4 (12.5)	12 (33.33)	0.03
1	16 (50)	22 (61.11)	
2	10 (31.25)	2 (5.55)	
3	2 (6.25)	0 (0)	
>3	0 (0)	0 (0)	
Total oral analgesic consumption in 1st 48 h postoperative (mg)	191.07±90.80	163.83±114.52	0.348NS

Data are represented as mean±SE, range or frequency. $P<0.05$ versus group CK, NSNonsignificant. SE: Standard error; CK: Caudal ketamine; TK: Topical ketamine

Table 5: Perioperative adverse events

Item	Group CK ($n=32$) (%)	Group TK ($n=36$) (%)	*P*
Hypotension	-	2 (5.9)	0.231NS
Bradycardia	2 (6.3)	2 (5.9)	0.670NS
Fever	4 (12.5)	0	0.04
Urine retention	4 (12.5)	0	0.04
Photophobia	2 (6.3)	0	0.231NS
Emergence agitation	0	0	NA
Residual motor block	2 (6.3)	0	0.231NS

Data are represented as number and frequency. $P<0.05$ versus group CK, NSNonsignificant; NA: Not applicable; CK: Caudal ketamine; TK: Topical ketamine

Table 6: Four-point Likert family satisfaction scale

Item	Group CK ($n=32$) (%)	Group TK ($n=36$) (%)	*P*
1 - excellent	18 (56.25)	26 (72.22)	0.000
2 - good	8 (25)	10 (27.78)	
3 - fair	6 (18.75)	0 (0)	
4 - poor	0 (0)	0 (0)	

Data are represented as number and frequency. $P<0.05$ versus Group CK; CK: Caudal ketamine; TK: Topical ketamine

First are the complications of the technique itself including failure, needle trauma, systemic toxicity, retention of urine, residual postoperative motor weakness, etc., Children are rarely subjected to detailed assessment after day-case surgery and there is a potential to underestimate the rate of complications.[21] This is particularly important in neonates and infants, who may not only be more susceptible to perturbations in neural development but who are also unable to report sensory symptoms and as they are not walking,

subtle motor deficits may be missed. Second is the neurotoxic effect of caudally administered drugs. The neuraxial route of delivery exposes local tissues (meninges, roots, and spinal parenchyma) to extraordinary concentrations of an agent (mg/mL), which because of local restrictions in redistribution may persist for extended intervals. Clinical studies are well suited to assess tolerability and efficacy but cannot reliably confirm safety and absence of morphological or neurological effects.[22]

The neurotoxic effects of ketamine after intrathecal administration were observed in animal studies[23] and after continuous intrathecal administration for the management of neuropathic cancer pain.[24] Consequently, its administration in the epidural space has been seriously questioned recently,[25] and the use of neuraxial ketamine for pediatric postoperative analgesia is decreasing in some countries.[26] Although no major neurological complications after a single dose of 0.25–0.5 mg/kg ketamine were observed,[27] preclinical safety studies and larger long-term epidemiological trials investigating possible neurological complications after CK administration are warranted, and topical administration of ketamine could be a safe alternative.

Our aim is not to discourage the use of neuraxial anesthesia but rather to investigate for other effective yet less invasive substitutes for postoperative pain relief. The indications for caudal analgesia in pediatric day case surgeries should be reviewed, and anesthetists are required to evaluate the relative risks and benefits of techniques, interventions, and drugs for each individual patient on a daily basis.

Conclusion

This study confirms the safety and analgesic effectiveness of precise administration of lower volumes of LAs (0.3 ml/kg) and ketamine 0.5 mg/kg through the local wound instillation. This noninvasive, simple, and inexpensive method for postoperative analgesia could be a safe alternative to caudal analgesia in children undergoing day-case herniotomy operations.

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Conflicts of interest

There are no conflicts of interest.

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