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Comparison of Analgesic Efficacy of Caudal Ropivacaine and Ketamine Vs. Ropivacaine and Midazolam in Paediatric Patients Undergoing Infraumbilical Surgery

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Abstract

Introduction: Caudal analgesia is a part of multimodal approach to acute and chronic pain management in children. Pain is associated with increase pain perception in subsequent painful neurohormonal, behavioural responses which can be harmful. Caudal blockade is the commonest regional technique used in children.

Objective: To assess the comparison of analgesic efficacy of caudal ropivacaine and ketamine vs ropivacaine and midazolam in paediatric patients undergoing infraumbilical surgery.

Methods: A randomised controlled trial was conducted at Dept. of Anesthesia, tertiary care hospital in Dhaka, Bangladesh from January to June 2021. Total 60 paediatric patients undergoing infraumbilical surgery included. Each group comprises of 30 patients, age between one to seven years, either gender, 8 to 25 kg and ASA I to III. Paediatric patients of ASA status IV and V, emergency surgeries, local infection of the caudal area, history of allergic reactions to local anaesthetics, bleeding diathesis, pre-existing neurological or spinal diseases, mental retardation, neuromuscular disorders were excluded from the study.

Results: Total 60 Paediatric Patients included. The patients demographics, ASA classifications, base line mean values in SBP, DBP, MAP, PR, RR, SpO2 and temperature, and mean duration of surgery in the groups were comparable. From the distribution of surgeries done across the two groups, in group A RK 15 patients (50%) had herniotomy, 12 patients (40%) had orchidopexy and 3 patients (10%) had hypospadias repair. In group B RM, 16 patients (53.3%) had herniotomy, 9 patients (30%) had orchidopexy and 5 patients (16.7%) had hypospadias repair. Only 3 subject (10%) in group B experienced fever and vomiting p=0.36. The TTFAR for groups A 14.4±2.36 hours and group B 12.0±3.69 hours were respectively. The values were significantly different between groups A and B (p=0.02). Total postoperative acetaminophen consumption in 24 hours was 102.67±89.62 mg, 118.59±98.71 mg for groups A and B respectively. Postoperatively, the mean FLACC pain scores at 30 minutes, 2, 4, 6 and 12 hours; the corresponding p values across the two groups, p=0.13, 0.00, 0.00, 0.00 and 0.03, show statistically significant difference in the scores at 2, 4, 6 and 12 hours.

Conclusion: The duration of postoperative analgesia along with time for first request of analgesic was comparatively superior in the Ropivacaine and ketamine combination rather than ropivacaine and midazolam without significant adverse effects or derangement in haemodynamic parameters. Despite unanswered questions exist, ketamine can be safely used as an adjuvant for caudal block in pediatrics for postoperative pain management to extend analgesic duration provided by local anesthetics alone with rare side effects. This adjuvant also decreases postoperative opioid consumption by prolonging the first analgesic requirement time.

Keywords: Analgesic, Efficacy, Paediatric Patients, Infraumbilical Surgery

Introduction

Regional anaesthesia in children is getting more popularities over the past few decades as it reduced the use of mysterious drug and it provides better stability. Caudal analgesia is a part of multimodal approach to acute and chronic pain management in children [1]. Pain is associated with increase pain perception in subsequent painful neurohormonal, behavioural responses which can be harmful [2]. Caudal blockade is the commonest regional technique used in children [3, 4, 5]. It produces dense, excellent peri-operative analgesia with minimal side effect. The technique is relatively reliable, simple, safe, very effective and easy to perform [6, 7].

Very minimum hemodynamic changes are seen after caudal block in children comparing to adults. Reasons are vasodilated systemic vasculature and low circulatory volume in legs and splanchnic system [8]. Historically, children have been undertreated for pain and painful procedures. Although caudal epidural block was described by Campbell in 1933 [9], it has evolved to become the most popular regional anaesthetic technique for intra- and post-operative pain relief in children from the 1980s. Caudal block is probably the most easily learned and mastered technique of all regional anaesthetic procedures [10, 11]. A major limitation of this technique is the relatively short duration of post-operative analgesia even with long-acting local anaesthetics. Prolongation of analgesia with caudal technique has been achieved with addition of various adjuvants to local anaesthetic agents, opioids being the most widely used adjuvant medication. Some of these newer agents such as dexmedetomidine have unwanted haemodynamic effects. Postoperative pain has become an even more important concern in pediatric age group. Choosing an anesthetic approach that provides the flexibility of extending analgesia into the postoperative period without any great risk of anesthetic neurotoxicity as well as ensures optimal intraoperative sensory and motor blockade is of paramount importance. Caudal anesthesia has gained the reputation of providing a reliable pain relief option postoperative. Opioids were commonly used adjuvants to prolong the analgesic effects. Unfortunately, several side effects have been reported associated with caudal opioids. These are nausea, vomiting, pruritis, urinary retention, and hypoventilation [12]. Respiratory depression may occur due to the rostral spread of opioids, leading to depression in the medullary respiratory center [13]. In caudal opioids, either alone or in conjunction with local anesthetics, the patient should be monitored at least 24 hours after surgery as the period during which the child is at risk of hypoventilation is unknown [14]. The quest for the optimal medication combination for caudal anesthesia is ongoing. Dexmedetomidine is a selective alpha-2 receptor agonist. It has analgesic and anxiolytic characteristics with minor adverse effects. Midazolam is a benzodiazepine that has anxiolytic, sedative, and anticonvulsant effects. Its analgesic effects are mediated by gamma-aminobutyric acid-benzodiazepine receptors in the spinal cord [15]. As an adjunct in the caudal block, midazolam is believed to extend the duration of analgesia [16]. There is a paucity of literature comparing analgesia, sedation, and side effects of these two non-opioid adjuvants (midazolam and dexmedetomidine) with ropivacaine in the caudal block [17]. As a result, we would want to examine the use of these adjuvants in conjunction with caudal ropivacaine for children undergoing infraumbilical surgeries. However, single-shot blocks have a limited duration of action which depends on the volume and concentration of the drug used. The duration of action can be prolonged either by addition of additives or by placing catheters for continuous analgesia. Placing catheters requires expertise and also greater postoperative care to prevent catheter migration intrathecally or into a blood vessel. Addition of adjuvant drugs allows the anesthesiologist to exploit the full potential of caudal and without the risk of anesthetic toxicity.

Materials and Methods

A randomised controlled trial study was conducted at Dept. of Anesthesia, tertiary care hospital, Dhaka, Bangladesh January to June 2021. Total 60 paediatric patients undergoing infraumbilical surgery were enrolled in the study. Each group comprises of 30 patients, age between one to seven years, either gender, 8 to 25 kg and ASA I to III. Paediatric patients of ASA status IV and V, emergency surgeries, local infection of the caudal area, history of allergic reactions to local anaesthetics, bleeding diathesis, pre-existing neurological or spinal diseases, mental retardation, neuromuscular disorders were excluded from the study.

Children were monitored for ECG, NIBP, SpO_2, temperature & $EtCO_2$. Intravenous premedication inj. glycopyrrolate 0.004 mg/kg was given. Induction of anaesthesia was done using inhalation method 100% oxygen with Sevoflurane 2 to 7%. I-gel insertion was facilitated by inj. succinyl choline 2 mg/kg. Anaesthesia was maintained with 50% O_2, 50% N_2O, Sevoflurane (1 to 2%) and inj. atracurium 0.5 mg/kg. Random selections done by close envelop method. Anaesthesiologist who did caudal block was unaware of the drug injected. Caudal epidural was performed with 22 gauze epidural needle under complete aseptic precaution with child in a left lateral position. After confirmation and negative aspiration for blood and CSF, the study drugs were injected.

Ropivacaine + ketamine group A RK,
Ropivacaine + midazolam group B RM.

Patients enrolled into the study were randomly divided into two groups by Group A - 1.0 ml/kg, 0.15% ropivicane with 0.3 mg/kg of Ketamine and Group B - 1.0 ml/kg, 0.15% ropivicane with 0.03 mg/kg of Midazolam. On the day of surgery, in the operation theatre, peripheral venous access was secured and monitors for vital parameters (heart rate, Electrocardiogram, Blood pressure, pulse oximeter) were attached. The co-induction agent was prepared in a 5 ml syringe by another Anesthesiologist or Anesthetic assistant who did not take part in the study.

Intra-operatively no analgesia was supplemented. Perioperative hemodynamic parameters NIBP, heart rate, SpO2 and EtCO2 were recorded at every 15 minutes till end of surgery. During surgery adequate analgesia was evaluated by hemodynamic changes (change in heart rate and systolic blood pressure at above or below 15% of baseline values) and requirement of sevoflurane concentration. An increase in heart rate and systolic blood pressure after 15 to 20 minutes of caudal block was considered as a failure of caudal anaesthesia. At the end of surgery, neuromuscular blockade was reversed with inj. neostigmine 0.05 mg/kg and inj. glycopyrrolate 0.008 mg/kg. Duration of surgery, duration of anaesthesia, requirement of inhalation agent and complications like bradycardia, tachycardia, hypotension, hypertension, vomiting and delayed motor recovery were recorded. Postoperative pain was evaluated by using FLACC score (maximum score of 10) (Table 1) at one hour interval for first three hours and thereafter every two hours interval till score more than three for 24 hours and rescue analgesic was given.

Table 1: FLACC postoperative pain score.

Categories	Scoring 0	Scoring 1	Scoring 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position. Moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry, (awake or asleep)	Moans or whimpers; Occasional complaint	Crying steadily, screams, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touch or hugging or being talked to	Difficulty to console or comfort

Statistical Analysis: Data were described as mean ± SD and percentages. For comparing data between two groups, unpaired student t test was used and p value < 0.005 calculated using IBM-SPSS (Statistical Package Social of Sciences) software. p-value <0.05 was interpreted as clinically significant.

Results

Table 2: Demographic characteristics, ASA, baseline vital signs and mean duration of surgery (N=60)

Variables	Group A (n=30)	Group B (n=30)	p value
Age (years)	2.9±1.06	2.8±1.08	0.95
Weight (kg)	17.2±4.47	16.8±3.76	0.73
Gender (M:F) - Number (%)	28:2 (93.3:6.7)	27:3 (90:10)	0.66
SBP (mmHg)	112.8±10.51	115.2±8.32	0.47
DBP (mmHg)	70.4±8.32	71.1±7.52	0.90
MAP (mmHg)	82.8±6.49	83.4±5.80	0.89
PR	102.3±10.05	105.7±10.23	0.54
SP02	99.9±0.21	99.8±0.53	0.25
Temp. (ºC)	36.9±0.25	37.0±0.23	0.16
ASA I	28 (93.3)	27 (90.0)	0.89
ASA II	2 (6.7)	3 (10.0)	0.99
Mean duration of surgery in minutes	50.82±33.20	50.95±30.89	

Data are expressed as mean ± SD or as number (%)

The patients demographics, ASA classifications, base line mean values in SBP, DBP, MAP, PR, RR, SpO_2 and temperature, and mean duration of surgery in the groups were comparable (Table 2).

Table 3: Distribution of surgeries across the three groups (N=100)

Surgeries	Group A (n=30)	Group B (n=30)
Herniotomy	15 (50%)	16 (53.3%)
Orchidopexy	12 (40%)	9 (30%)
Hypospadias repair	3 (10%)	5 (16.7%)

Data are expressed as number (%)

From the distribution of surgeries done across the two groups (Table 3), in group A 15 patients (50%) had herniotomy, 12 patients (40%) had orchidopexy and 3 patients (10%) had hypospadias repair. In group B, 16 patients (53.3%) had herniotomy, 9 patients (30%) had orchidopexy and 5 patients (16.7%) had hypospadias repair.

Table 4: Time to first analgesic request and total 24 hours analgesic consumption in each of the groups (N=100)

Item	Group A (n=25)	Group B (n=25)	Post-hoc P value
Mean analgesic duration (hours)	14.4±2.36	12.0±3.69	0.02*, 0.001*
Total 24 hrs. fentanyl (µg)	17.17±4.47	17.83±5.20	1.00, 0.192
Total 24 hours acetaminophen (mg)	102.6±89.62	118.59±98.71	0.761, 0.0012*

Data are expressed as mean ± SD. *Statistically significant

The TTFAR for groups A 14.4±2.36 hours and group B 12.0±3.69 hours were respectively. The values were significantly different between groups A and B (p=0.02). The corresponding mean total postoperative fentanyl consumptions in 24 hours were 17.17±4.47 µg, 17.83±5.20 for groups A, B, while the mean total postoperative acetaminophen consumption in 24 hours was 102.67±89.62 mg, 118.59±98.71 mg for groups A and B respectively. Post-hoc analysis revealed that there was also statistically significant difference in acetaminophen consumption between groups A and B (p=0.001) (Table 4).

Table 5: Postoperative pain assessment using FLACC score at different time points (N=100)

Pain assessment (FLACC)	Group A (n=30)	Group B (n=30)	p-value
30 minutes	0.1±0.35	0.3±0.48	0.13
2 hours	0.3±0.48	0.5±0.51	0.00*
4 hours	0.5±0.67	1.0±0.79	0.00*
6 hours	0.6±0.59	1.9±1.21	0.00*
12 hours	0.6±1.40	1.3±1.62	0.03*

*Statistically significant

Postoperatively, the mean FLACC pain scores at 30 minutes, 2, 4, 6 and 12 hours are shown in Table 5; the corresponding p values across the two groups, p=0.13, 0.00, 0.00, 0.00 and 0.03, show statistically significant difference in the scores at 2, 4, 6 and 12 hours.

Table 6: Postoperative complications among groups in the study (N=100)

Complications	Group A (%) n=30	Group B (%) n=30	p value
Vomiting			
Yes	0 (0.0)	2 (6.7)	0.36
No	30 (100.0)	28 (93.3)	
Fever			
Yes	0 (0.0)	3 (10)	0.36
No	30 (100.0)	27 (90)	

Only 3 subject (10%) in group B experienced fever and vomiting p=0.36 (Table 6).

Discussion

This study shows that the addition of ketamine to caudal ropivacaine in children undergoing ambulatory groin surgery results in significant prolongation of analgesia and reduces analgesic consumption in the first 24 hours post operatively. The important goal in paediatric patient is to provide effective postoperative analgesia for considerable duration. It is difficult to differentiate restlessness or crying due to pain or fear [16]. Caudal blockade is commonly used as popular regional technique in children. It is simple and safe and produces dense peri-operative analgesia with high success rate [17, 18]. Patients enrolled into the study were randomly divided into two groups by Group A - 1.0 ml/kg, 0.15% ropivicane with 0.3 mg/kg of Ketamine and Group B - 1.0 ml/kg, 0.15% ropivicane with 0.03 mg/kg of Midazolam. On the day of surgery, in the operation theatre, peripheral venous access was secured and monitors for vital parameters (heart rate, Electrocardiogram, Blood pressure, pulse oximeter) were attached. Up to eight hours postoperatively, mean FLACC score was less than three in group A compared to group B. Ropivacaine is a new amide local anaesthetic having similar profile to equipotent doses of bupivacaine [19]. It provides excellent postoperative analgesia by epidural or perineural approach. It has less intrinsic toxicity, so its margin of safety increases compared to other local anaesthetics [20]. Ketamine added local anesthetics versus other adjuvants added local anesthetics. Compared to other adjuvants, such as dexamethasone, fentanyl, morphine, and adrenaline, adding ketamine to local anesthetics for a caudal block controlling childrens' postoperative pain is a recent developing trend. Adding neostigmine, midazolam, and ketamine to bupivacaine alone for caudal block in children results in decreased quantity of rescue analgesia. Increased time to initial rescue analgesic administration compared to pure ropivacaine at the same time, there were no significant differences in the number of complications that happened in the first 24 hours of the postoperative period between the four study groups [21]. Ketamine showed to be superior in prolonging the duration of analgesia and blunting neuroendocrine stress response without side effects than fentanyl when added to ropivacaine for caudal block in children who underwent infraumbilical surgery [22, 23]. Extension of analgesia duration from ketamine added local anesthetics in a caudal block is also superior to magnesium sulfate added local anesthetics [24]. The TTFAR for groups A 14.4±2.36 hours and group B 12.0±3.69 hours were respectively. The values were significantly different between groups A and B (p=0.02). The corresponding mean total postoperative fentanyl consumptions in 24 hours were 17.17±4.47 µg, 17.83±5.20 for groups A, B, while the mean total postoperative acetaminophen consumption in 24 hours was 102.67±89.62 mg, 118.59±98.71 mg for groups A and B respectively. Furthermore, in comparison with group B, a significantly longer TTFAR was found in group A. However, the incidence of adverse effects was comparably minimal in all the two groups. Without the addition of adjuvants, the use of a local anaesthetic is limited by its duration of action and dose dependent side effects [25]. In this study, group B had the shortest duration of analgesia and a pain score of ≥4 was achieved earliest compared to groups A and B. However, the observation by Xiang *et al*. could not preclude the effects of ketamine [26]. For the avoidance of confounding variable Ketamine was not administered to subjects in this study. A dose of 1.0 ml/kg, 0.15% ropivacaine was administered in this study. Though this is lower than that in the study by Goyal *et al*. who used 1.0 ml/kg, 0.15% ropivacaine, the postoperative analgesic durations are comparable [27]. Midazolam 0.03 mg/kg as caudal adjuvant could be considered as optimal deducing from the documentation by de Beer *et al*., Kumar *et al*. and Gulec *et al*. alike, using similar caudal midazolam dose of 0.03 mg/kg, reported comparatively longer analgesic durations of 16.8±3.9 hours and 21.15±1 hours respectively [28, 29]. Undoubtedly, the observation by Kumar *et al*. is attributable to the use of 70% nitrous oxide and a higher dose 1.0 ml/kg, 0.15% ropivacaine combined with 50 µg/kg midazolam [28]. In the case of Gulec *et al*. the prolonged sedation recorded in their ropivacaine and midazolam group could underpin their observation of a much longer analgesic duration, as sedation could easily be swapped for analgesia in nonverbal children [29]. Abodesira *et al*. administering caudal 0.5 ml/kg ropivacaine combined with midazolam 50 µg/kg reported a shorter TTFAR (5.20 hours), further supporting Verghese *et al*., [30] another reason for the greater analgesic duration observed in group A relative to group B would be the dissimilar binding affinities exhibited by the two drugs toward their respective receptors. Significantly higher FLACC scores were recorded from 2 hours postoperatively in Group B, denoting sooner waning analgesic effect of caudal ropivacaine with adjuvant midazolam. Agreeably, a significant difference in 24 hours acetaminophen consumption was observed between groups A and B such was not recorded in 24 hours fentanyl consumption across the groups in this study. This indicates that repeated assessment of pain and repeated dosing of analgesic over a longer duration might be better reflective of actual analgesic consumption than a single pain assessment and analgesic dose. The reduced total analgesic consumption observed in Group A further agrees with the finding by Salama *et al*., [31] though Baris *et al*. in their study found no difference in analgesic requirement across the groups, they admitted the advantage in ropivacaine with adjuvant combination over ketamine alone during caudal block for more painful surgeries [32]. This study recorded 10% incidence of vomiting and fever which occurred 5 hours postoperatively in one patient in Group B only. The patient responded well to sponging with tepid water, acetaminophen treatment. Himabindu *et al*. in a similar study reported higher (18%) incidence of vomiting, most likely a consequence of the nitrous oxide used [33]. There are some limitations of the study. The doses of the two adjuvants chosen for comparison in the study might not be equipotent; a dose-response curve for each adjunct was not determined and the doses selected were based on previous studies with the assumption that such doses were optimal.

Conclusion

The duration of postoperative analgesia along with time for first request of analgesic was comparitavely superior in Ropivacaine and ketamine combination rather than Ropivacaine and midazolam combination without significant adverse effects or derangement in haemodynamic parameters. The clinical use, dosage, and effect of ketamine when used as an adjuvant for a pediatric caudal block for pain control after infra umbilical surgeries. Despite unanswered questions exist, ketamine can be safely used as an adjuvant for caudal block in pediatrics for postoperative pain management to extend analgesic duration provided by local anesthetics alone with rare side effects. This adjuvant also decreases postoperative opioid consumption by prolonging the first analgesic requirement time.

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