Introduction

Caudal epidural is an accepted and popular method of providing intra and postoperative analgesia for abdominal,
perineal, and lower limb surgeries in children.\textsuperscript{[1]} Bupivacaine is the most commonly used local anesthetic for this purpose.\textsuperscript{[2]} A major disadvantage of bupivacaine is the relatively short duration of postoperative analgesia for which opioids have traditionally been added to increase the duration of analgesia but have been associated with unacceptable side-effects.\textsuperscript{[3-5]} Clonidine, an alpha 2 agonist has extensively been used in neuraxial blocks and peripheral nerve blocks to prolong the action of bupivacaine.\textsuperscript{[6-9]} It is one of the most commonly used additives with bupivacaine for caudal analgesia in children.\textsuperscript{[10]} Midazolam is a water-soluble benzodiazepine that interacts with specific gamma-aminobutyric acid (GABA) receptors in the spinal cord and brain to modulate nociceptive responses.\textsuperscript{[10]} Based on earlier human studies, it is hypothesized that caudal midazolam would produce more postoperative analgesic effect with bupivacaine with minimal side-effects.\textsuperscript{[11-13]}

In view of paucity of studies comparing the efficacy of caudal clonidine and caudal midazolam in prolonging the duration of analgesia when added as adjuvants to bupivacaine\textsuperscript{[2] and due to the highly variable duration of analgesia produced by caudal midazolam bupivacaine mixtures in various studies,\textsuperscript{[11-13]} we attempted to compare the effect of midazolam with the previously established and commonly used adjunct clonidine on duration of postoperative analgesia when administered by caudal epidural route for infra-umbilical surgeries in children. Another primary objective was to assess the requirement of postoperative rescue analgesics. Secondary objectives to be assessed included: Intraoperative hemodynamic changes; postoperative sedation scores and any side-effects or complications.

Material and Methods

After obtaining Institutional Ethical Committee approval and written informed consent from the parents, this prospective, randomized, controlled, double-blinded, single-center study was conducted in 75 patients, American Society of Anesthesiologists physical status I-II, age 1-7 years, undergoing sub-umbilical surgeries under general anesthesia. Children with local infection of the caudal area, history of allergic reactions to local anesthetics, bleeding diathesis, preexisting neurological or spinal diseases, mental retardation, and neuromuscular disorders were excluded from the study.

The patients were randomly allocated into three groups: Group B (control group), Group BC (clonidine study group) and group BM (midazolam study group). Randomization was done by picking random lots from a sealed bag. Twenty minutes before shifting them to the operating theater, oral midazolam 0.5 mg/kg was administered as premedication to all the children. The patients were then shifted to the operating theater and connected to monitors; electrocardiogram, noninvasive blood pressure and pulse oximeter and baseline values were recorded. Anesthesia was induced with 50% nitrous oxide, 50% oxygen and 8% sevoflurane. Intravenous access was secured and lactated Ringer’s solution was administered as per the calculated fluid requirements. Airway management was left to the discretion of the attending anesthesiologist and the children were managed with face mask, laryngeal mask airway or endotracheal tube, with or without muscle relaxants. Anesthesia was maintained with 1-2% sevoflurane in oxygen–nitrous oxide (1:3) mixture. After induction, patients were placed in the lateral decubitus position and a single shot caudal epidural was performed, with aseptic precautions, using a 23 G hypodermic needle, by an anesthesiologist who was blinded to the drug that was to be administered in the caudal epidural space. The drug was loaded by an anesthesiologist who did not participate in the study. Group B patients received 1 ml/kg of 0.25% bupivacaine in normal saline, Group BC patients received 1 ml/kg of 0.25% bupivacaine with 1 µg/kg of clonidine in normal saline, and Group BM patients received 1 ml/kg of 0.25% bupivacaine with 30 µg/kg of midazolam in normal saline. The patients were extubated at the end of the procedure and the duration of anesthesia was noted in all the groups.

During intraoperative period, adequacy of analgesia was gauged by hemodynamic stability. Absence of rise of heart rate (HR) or mean arterial pressure (MAP) of more than 15% compared with baseline values recorded just before surgical incision was considered as adequate analgesia. An increase in HR or MAP (>15%), 15 min after administration of caudal anesthesia was defined as failure of analgesia. If HR, MAP increased 45 min after surgical incision it was considered as inadequate analgesia. Patients with failure of caudal analgesia or inadequate analgesia were given fentanyl 2 µg/kg intravenously. Patients, in whom caudal anesthesia failed or inadequate analgesia was present, were excluded from study.

The patients were continuously observed for 24 h postoperatively. Postoperative assessment was done by another anesthesiologist in the postanesthesia care unit (PACU) who was not aware of the drug administered and by a nurse in the ward who was also blinded. Pain score was assessed using the FLACC (F — face, L — leg, A — activity, C — cry, C — consolability) scale [Table 1].\textsuperscript{[14]} Assessment of pain by FLACC scale was done at 0, 1, 2, 6, 12 and 24 h postoperatively. The time from caudal placement of drug to the first recording of a FLACC score ≥4 was taken as the duration of analgesia.
In the PACU, the necessity for rescue medicine was decided by the pain score. Rescue medication was administered when patients had score of ≥4 on at least 2 occasions or showed obvious signs of pain. Paracetamol suppository was used as rescue medicine with a loading dose of 40 mg/kg followed by 20 mg/kg every 6 h.

The number of doses of rescue medication required and the time to first administration of rescue medication were also noted. The HR and blood pressure were measured at 5, 10, 15, 30, 45, 60, 90, and 120 min postoperatively. Sedation scores were recorded at 0, 1, 2, 4, 8, and 12 h after surgery using a 4 point sedation score [Table 2].

In the postoperative period, patients were also monitored for adverse effects, including respiratory depression, vomiting, hypotension and bradycardia. Respiratory depression was defined as a decrease in oxygen saturation <93%, requiring oxygen by face mask. Hypotension was defined as systolic blood pressure (SBP) <70 mm Hg and bradycardia was defined as a HR <80 beats/min.

Based on clinical experience and review of the literature, it was expected that a 60-min difference of mean duration of analgesia between any two groups would be statistically significant. Within group standard deviation was assumed to be 60. Using this data and assuming a study power of 90% and probability of type I error of 5%, a sample size of 25 patients per group was necessary for detecting clinically significant difference. Normally distributed continuous variables were compared using ANOVA. If the F value was significant and variance was homogeneous, Tukey multiple comparison test was used to assess the differences between the individual groups; otherwise Tamhane’s T2 test was used. The Kruskal–Wallis test was used for those variables that were not normally distributed and further comparisons were done using Mann–Whitney U-test. Categorical variables were analyzed using the Chi-square test. For all statistical tests, a P < 0.05 was taken to indicate a significant difference.

### Results

The study groups were comparable with respect to mean age, weight, gender, duration, and type of surgery [Tables 3 and 4].

The SBP and HR at induction, intraoperatively and postoperatively, when compared between the three groups using student t-test, yielded P > 0.05, which were not significant. Both SBP and HR decreased during anesthesia followed by an increase in postop period in all the groups, but the changes were not significant (P > 0.05) [Table 5].

Surgical analgesia in all the groups was found to be adequate. No patient in any group required intraoperative rescue analgesia. The pain score was assessed using the FLACC scale and the three groups were compared using Pearson’s Chi-square test. The FLACC pain score never reached ≥4 during the first 3 h in any of the groups. However, the number of patients with FLACC pain score ≥4 were significantly more in Group B at the end of 4th (46%), 8th (56%) and 12th (72%) h compared to the other two groups. Furthermore at the end of 12th h,

### Table 1: FLACC pain scale

| Parameter       | 0          | 1          | 2          |
|-----------------|------------|------------|------------|
| Face            | No expression | Occasional grimace | Frequent to constant quivering chin |
| Legs            | Normal position or relaxed | Uneasy, restless, tense | Kicking or legs drawn up |
| Activity        | Lying quiet | Squirming, shifting back and forth, tense | Arched, rigid or jerking |
| Cry             | No cry | Moans or whimpers | Crying steadily |
| Consolability   | Content, relaxed | Reassurance, hugging | Difficult to console |

*Score: 0, no pain; 1-3, mild pain; 4-7, moderate pain; 8-10, severe pain; FLACC: Face, legs, activity, cry, consolability*

### Table 2: Four (4) point sedation score

| Sedation score | Description                          |
|----------------|--------------------------------------|
| 1              | Asleep, not arousable by verbal contact |
| 2              | Asleep, arousable by verbal contact    |
| 3              | Drowsy not sleeping                   |
| 4              | Alert/awake                           |

### Table 3: Demographic and clinical data

| Variables                | Group B (n = 25) | Group BC (n = 25) | Group BM (n = 25) | P    |
|--------------------------|-----------------|------------------|------------------|------|
| Age (years)              | 6.64±1.29       | 6.28±1.21        | 6.16±1.11        | 0.346 (NS) |
| Weight (kg)              | 16.28±3.06      | 15.48±3.34       | 14.96±2.88       | 0.322 (NS) |
| Gender: Male:female ratio| 22:3            | 23:2             | 20:5             | 0.446 (NS) |
| Duration of anesthesia (min) | 101.72±6.70     | 103.22±5.46      | 100.58±3.57      | 0.485 (NS) |
| Baseline: HR (beats/min) | 103.56±5.52     | 102.92±8.67      | 105.48±7.92      | 0.458 (NS) |
| Baseline: SBP (mmHg)     | 100.64±6.29     | 98.84±6.20       | 101.52±5.17      | 0.269 (NS) |

*Data shown as mean ± SD. NS differences were noted between the groups. SD = Standard deviation, NS = No significant, HR = Heart rate, SBP = Systolic blood pressure*
the number of patients with FLACC pain score ≥4 were significantly more in Group BM (40%) compared to Group BC (8%). More children in Group B had moderate to severe pain at 4 h, 8 h and 12 h postoperatively, compared to children in Group BC and Group BM [Figure 1].

The duration of analgesia between the three groups was compared using Mann–Whitney test. The duration of analgesia was significantly prolonged with the addition of clonidine or midazolam to caudal bupivacaine (mean [95% confidence interval (CI)]: 725 [700-750] and 605 [580-630] min, respectively) compared to bupivacaine alone (mean [95% CI]: 295 [270-320] min) with \( P = 0.001 \) [Figure 2]. The requirement of rescue medications was compared between the three groups using Pearson’s Chi-square test and it was found to be significant with Group BC receiving less number of analgesics, followed by Group BM and Group B. One child in Group BC received three rescue medications compared to Group BM, in which 7 (28%) children received three rescue medications, followed by Group B where 15 (60%) children received three rescue medications [Figure 3].

The complications/side-effects seen in the three groups are shown in Table 6. The difference between the complications was statistically insignificant with the \( P \) value of >0.05. Mean sedation score in the immediate postoperative period was higher in Group B (2.84 ± 0.2688) compared to Group BC (1.88 ± 0.2112) and BM (1.76 ± 0.3648) with \( P = 0.001 \). Thereafter, there was a gradual rise in mean sedation score in all three groups. There was prolonged sedation in Group BC in comparison to Group BM with mean sedation scores of 3.72 ± 0.4032 and 3.96 ± 0.0768, respectively at 12 h postoperatively with \( P = 0.001 \) [Table 7].

**Discussion**

Caudal epidural anesthesia is a simple, frequently used technique, which provides very effective analgesia intra and postoperatively in pediatric patients undergoing infra-umbilical

**Table 4: Type of infra-umbilical surgeries performed**

| Type of surgery      | Group B | Group BC | Group BM |
|----------------------|---------|----------|----------|
| Herniotomy           | 14      | 12       | 13       |
| Circumcision         | 5       | 8        | 8        |
| Orchidopexy          | 2       | 2        | 3        |
| Urethroplasty        | 2       | 1        | 0        |
| Dermoid excision     | 1       | 0        | 0        |
| Fistula excision     | 0       | 2        | 0        |
| PUV excision         | 0       | 0        | 1        |
| Polyp excision       | 1       | 0        | 0        |

Values are in number of patients. PUV = Posterior urethral valves

**Figure 1:** The FLACC pain scores in the three groups. Patients with FLACC scores ≥4 were significantly more in Group B compared to Group BC and BM

**Figure 2:** Duration of analgesia in the three groups. Group B received 1 ml/kg of 0.25% plain bupivacaine, Group BC received 1 ml/kg of 0.25% bupivacaine with 1 µg/kg clonidine and Group BM received 1 ml/kg of 0.25% bupivacaine with 30 µg/kg midazolam. The mean duration of analgesia was 295 min in Group B, 724.8 min in Group BC and 605.4 min in Group BM

**Figure 3:** Trends in postoperative requirement of rescue analgesic. Values are in percentage of patients requiring 1, 2 or 3 doses of rescue analgesics. More patients in Group B (plain bupivacaine) needed three doses of rescue analgesics compared to patients in Group BC (clonidine with bupivacaine) and Group BM (midazolam with bupivacaine)
surgeries. The search for the ideal combination of drugs for caudal anesthesia in pediatric patients is on. Our study indicates that addition of both clonidine and midazolam are safe and efficacious in prolonging the duration of postoperative analgesia when administered as adjuvants via the caudal route in children undergoing lower abdominal surgeries; however, clonidine is more efficacious as it provides a longer duration of analgesia. Furthermore, postoperative rescue analgesic requirements are significantly less with the use of clonidine. Both the adjuvants are associated with minimal side-effects. Our findings are consistent with those reported by several other studies.[15-21]

In children, a mixture of 0.25% bupivacaine with 1-2 µg/kg clonidine has been seen to improve the duration and quality of analgesia provided by caudal analgesia. Although results differ widely, the duration of analgesia provided ranged from 6.3 h[20] to 16.4 h[15] for 1 µg/kg to 5.8[19] and 9.8 h[16] for 2 µg/kg. One study has shown a mean duration of analgesia of 20.9 ± 7.4 h in children receiving caudal clonidine with bupivacaine, but a and quality of analgesia has been noted with caudal midazolam but with wide variations in results.[11-13,22] The wide variation in the duration of action of clonidine or midazolam in the various studies could be due to many reasons: Dose of clonidine used, differences in premedication and volatile anesthetic used, type of surgery, indications for rescue analgesia, assessment of pain, and statistical analysis. In our study, the duration of analgesia in Group BC was 12 h, in Group BM it was 10 h and in Group B it was 5 h, which was similar to other studies. Although many studies have supported the analgesic benefits of caudal clonidine as an additive, there are some studies that have shown that there is no such benefit.[23-25]

Several mechanisms have been suggested for the clonidine-induced prolongation of caudal analgesia with bupivacaine. The anti-nociceptive action is due to the direct suppression of spinal cord nociceptive neurons by epidural clonidine. Clonidine also suppresses neurotransmission in peripheral sensory Aδ and C nerve fibers.[26] Caudal midazolam exerts its analgesic effect through the GABA-benzodiazepine system in the spinal cord. Benzodiazepine binding sites have been demonstrated in the spinal cord, particularly within lamina II of the dorsal horn, and appear to be linked to the GABA-A receptor complex. Furthermore, endogenous benzodiazepine-like substances have been isolated from human cerebrospinal fluid.[27,28]

### Table 5: Intraoperative vitals

| Intraoperative vitals | Group B | Group BC | Group BM | P       |
|-----------------------|---------|----------|---------|---------|
| HR before induction (beats/min) | 103.56±5.52 | 102.92±8.67 | 105.48±7.92 | 0.458 (NS) |
| Intra-operative HR     | 92.60±6.19  | 97.36±6.50  | 99.60±8.15  | 0.598 (NS) |
| Postoperative HR       | 97.92±6.36  | 98.68±6.87  | 100.20±7.62 | 0.380 (NS) |
| SBP before induction (mmHg) | 100.64±6.29 | 98.84±6.20  | 101.52±5.17 | 0.269 (NS) |
| Intra-operative SBP    | 95.92±6.01  | 94.96±6.01  | 95.20±7.39  | 0.831 (NS) |
| Postoperative SBP      | 97.20±7.39  | 96.40±3.42  | 99.76±6.31  | 0.359 (NS) |

Data shown as mean±SD. NS differences were noted between the groups. SD = Standard deviation, NS = No significant, HR = Heart rate, SBP = Systolic blood pressure

### Table 6: Complications/side-effects

| Complication/side-effects | Group B (%) | Group BC (%) | Group BM (%) | P       |
|---------------------------|-------------|--------------|--------------|---------|
| Nausea/vomiting           | 0 (0)       | 0 (0)        | 1 (4)        | 0.807 (NS) |
| Respiratory depression    | 0 (0)       | 1 (4)        | 1 (4)        | 0.764 (NS) |
| Bradycardia               | 0 (0)       | 1 (4)        | 0 (0)        | 0.363 (NS) |
| Hypotension               | 0 (0)       | 0 (0)        | 1 (4)        | 0.598 (NS) |

Values are in n (%) of patients. NS differences were noted between the groups. NS=No significant

### Table 7: Postoperative mean sedation score

| Postoperative time (h) | Mean sedation score | P       |
|------------------------|---------------------|---------|
|                        | Group B | Group BC | Group BM | B and BC | B and BM | BC and BM |
| 0                      | 2.84±0.2688 | 1.88±0.2112 | 1.76±0.3648 | 0.001 | 0.001 | 0.161 |
| 1                      | 3.44±0.4928 | 2.24±0.3648 | 2.36±0.4608 | 0.001 | 0.001 | 0.312 |
| 2                      | 3.56±0.4928 | 2.6±0.48 | 2.72±0.4032 | 0.001 | 0.001 | 0.343 |
| 4                      | 3.8±0.32 | 3.08±0.2208 | 3.16±0.2688 | 0.001 | 0.005 | 0.256 |
| 8                      | 4±0.0 | 3.12±0.2816 | 3.56±0.4928 | 0.002 | 0.006 | 0.001 |
| 12                     | 4±0.0 | 3.72±0.4032 | 3.96±0.0768 | 0.006 | 0.012 | 0.001 |

Data shown as mean±SD. SD=Standard deviation
The dose of clonidine for epidural administration is 1-5 µg/kg.\textsuperscript{[13,19,21]} We chose a dose of 1 µg/kg of clonidine in our study as there were studies showing that increasing the dose from 1 to 2 µg/kg did not enhance the analgesic efficacy of clonidine,\textsuperscript{[29]} but the incidence of adverse effects such as respiratory depression, bradycardia and hypotension increased with increasing dose.\textsuperscript{[30]} The dose of caudal midazolam used in most of the previous studies as mentioned above is 50 µg/kg.\textsuperscript{[11,13]} Although most studies suggest that this dose is associated with a prolonged postoperative analgesia with minimum sedation and vomiting but some studies mention otherwise.\textsuperscript{[12,31]} Hence, we decided to administer caudal midazolam in a dose of 30 µg/kg. The reason that we had chosen a standard dose of 1 mL/kg of 0.25% bupivacaine as the final volume in all the groups was based on the speculation that smaller volumes of bupivacaine may not be enough to deliver the adjuvants up to the spinal cord.\textsuperscript{[25]}

The use of both caudal clonidine and midazolam has been associated with clinically insignificant respiratory or hemodynamic effects.\textsuperscript{[11-13,32]} Although hemodynamic side-effects appear to be less pronounced in children than in adults, they may be dose-dependent, as reported by Motsch et al.\textsuperscript{[21]} One case of life-threatening apnea following inguinal herniorrhaphy and orchidopexy, in a 2 weeks old term neonate with the use of clonidine has been reported.\textsuperscript{[30]} Although 1 patient of Group BC and 1 patient of Group BM developed bradycardia and hypotension, respectively, but it was statistically insignificant.

A sedative effect has been observed after epidural clonidine and midazolam in adults\textsuperscript{[33,34]} and to a lesser degree in children.\textsuperscript{[11,15,16]} Many previous studies have, however, not reported respiratory depression after caudal administration of midazolam or clonidine.\textsuperscript{[15,16,35]} One study found that the duration of sedation was very similar to the respective duration of caudal analgesia with clonidine.\textsuperscript{[16]} The sedation score in our study also correlated well with the duration of analgesia in Group BC and BM with no incidence of respiratory depression. The longer duration of sedation in Group BC compared to BM resulted partly from the sedative effect of clonidine and partly from the longer duration of analgesia provided by clonidine.

One patient out of 25 had vomiting in the Group BM, but no patient of Group B or BC had vomiting in the postoperative period. Both clonidine and midazolam have been shown to possess anti-emetic properties when administered intravenously.\textsuperscript{[36,37]} We chose the FLACC scale to evaluate pain postoperatively as it is easy to use, is validated and gives us an objective evaluation.\textsuperscript{[14]} One limitation of our study was that we did not assess the mean time of arousal from anesthesia in any of the groups.

We conclude that both clonidine in a dose of 1 µg/kg and midazolam in a dose of 30 µg/kg added to 0.25% bupivacaine for caudal analgesia and administered as a 1 mL/kg mixture in children, for sub-umbilical surgery, significantly prolongs the duration of postoperative analgesia when compared to 1 mL/kg of 0.25% bupivacaine alone, without any side-effects.

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Conflicts of interest
There are no conflicts of interest.

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