Original Article

# Effect of adding midazolam to intrathecal bupivacaine in children undergoing lower abdominal surgeries: A randomised controlled trial

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## ABSTRACT

**Background and Aims:** Avoidance of general anaesthesia for short-duration surgeries is a prerequisite, especially for children. Spinal anaesthesia is established as an appropriate anaesthetic procedure for this target. Midazolam has been proven to be safe for children as premedication. This study aimed to evaluate the effects of adding midazolam to intrathecal bupivacaine on intraoperative quality, duration of spinal anaesthesia and postoperative (PO) analgesia for children undergoing lower abdominal surgeries. **Methods:** A prospective, comparative interventional study included 120 paediatric patients who were randomly divided into two groups that received intrathecal bupivacaine plus normal saline (B/S) or intrathecal bupivacaine plus midazolam (B/M). The efficacy of PO analgesia was assessed using the observational pain–discomfort scale (OPS). Duration of PO analgesia was measured, and recovery of motor block was assessed every 30 min till the Bromage scale reached 0. The level of PO sedation was assessed using the modified Wilson Sedation Score (WSS). Results were analysed using the one-way analysis of variance (ANOVA) test, Mann–Whitney test and Chi-square test. **Results:** Onset of sensory and motor blocks was significantly faster, and the frequency of patients having Bromage score of 3 within ≤10 min was significantly higher in group B/M than group B/S. Durations till sensory and motor recovery were significantly longer, the number of requests for PO analgesia was significantly lower and the mean of WSS was significantly higher at 30 and 120 min in group B/M than group B/S. **Conclusion:** Intrathecal bupivacaine–midazolam combination significantly prolonged the duration of spinal anaesthesia and provided prolonged PO analgesia.

**Key words:** Bupivacaine, intrathecal injection, midazolam, paediatric, pain, postoperative

## INTRODUCTION

Paediatric spinal anaesthesia is a safe alternative to general anaesthesia and can be the anaesthetic technique of choice in many lower abdominal procedures in children.[1] An adjuvant is a drug which acts synergistically with a local anaesthetic (LA) to improve the value of the block and postoperative (PO) analgesia and to overcome the drawback of the short duration of spinal anaesthesia in children.[2] Numerous adjuvants had been tried including opioids, but their use is limited by opioid-related adverse effects, especially with neuraxial use.[3]

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that mediates neuronal suppression, including the spinal cord. Benzodiazepines bind to and act on α1–3- and α5-containing GABA receptors. Midazolam hydrochloride is a short-acting



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benzodiazepine derivative with an imidazole structure.[4] Midazolam is a common drug that is familiar to physicians for its anxiolytic, amnestic, hypnotic, anticonvulsant and sedative properties.[5] This study was aimed to evaluate the quality of spinal anaesthesia and PO analgesia affected by adding midazolam as an adjuvant to bupivacaine intrathecal anaesthesia for lower abdominal surgeries in children.

## METHODS

The study was a prospective and randomised controlled clinical trial. It was conducted from January 2020 to March 2021 after obtaining approval from the Institutional Review Board (IRB) under the IRB code (ALEM6_RE_04_19), registered under clinical trials. gov ID (NCT 04718259), and informed consent taken from the patients' parents.

One hundred and twenty paediatric patients of both genders were enroled in this study. Inclusion criteria were patients with the American Society of Anesthesiologists (ASA) physical status class I, age between 3 and 12 years, body weight between 15 and 42 kg and those scheduled for lower abdominal and/or pelvic surgeries. Exclusion criteria were congenital anomalies, especially of the spine, skin infections in the back, coagulation disorders or allergy to the drugs of the study, fever and common cold on admission and parental refusal. All patients were evaluated preoperatively in the pre-anaesthesia clinic, explained the technique of anaesthesia and the patients' demographic data (age in years, gender and weight in kg) were recorded.. On arrival at the hospital, body temperature was measured and children who had manifestations of fever or common cold were postponed.

Patients were randomly divided into two groups (B/S and B/M) using coloured cards: red and yellow. Cards were previously prepared by an assistant who was blinded about the colour significance. The child or the parent was allowed to choose one of these cards, and the anaesthetist did not attend during card choice. Study drugs were prepared by another anaesthetist who was blinded to patients' choice. Group B/S received bupivacaine plus normal saline (control group) intrathecally, while group B/M received bupivacaine plus midazolam intrathecally (interventional group).

On arrival into the operating theatre, children were monitored for electrocardiography, heart rate (HR), non-invasive blood pressure (NIBP), oxygen saturation ($SpO_2$) and end-tidal carbon dioxide. After that, all children were cannulated and preloaded with intravenous infusion of Ringer's lactate solution (10 ml/kg), premedicated with intramuscular injection of atropine sulphate (0.01 mg/kg) or glycopyrrolate (4 μg/kg) according to availability and sedated with ketamine hydrochloride (1 mg/kg) to keep them immobile during a lumbar puncture.

All patients received spinal anaesthesia via midline approach in the left lateral position with flexed hips and knees. Under the aseptic technique, the skin of the back was sterilised with 0.5% chlorhexidine in alcohol and then covered by a sterile drape. Lumbar puncture was performed in L4–L5 interspace using a standard 25 G or 27 G, 9-cm Quincke spinal needle with stylet, and the bevel was directed in parallel to the longitudinal dural fibres. After getting a free flow of cerebrospinal fluid, 0.5% hyperbaric bupivacaine in a weight-dependent dose (0.4 mg/kg for children weighing 5–15 kg and 0.3 mg/kg for children weighing >15 kg) was given in both groups, which was followed by either 0.5 ml of normal saline in group B/S (Control group) or 0.5 mg (i.e. 0.5 ml from 2 mg/2 ml ampoule) preservative-free midazolam (Dormicum; Hoffman-La Roche, Basel, Switzerland) intrathecally in group B/M.[3]

Immediately after removal of the spinal needle, a sterile dressing was applied and patients were turned to supine position. Time at the end of injection was recorded and considered as time zero for further data recording. Surgeries were performed under spinal anaesthesia, and all patients were sedated with intravenous propofol infusion at a rate of 50–75 μg/kg/min and the infusion rate was adjusted to keep the child in a state of moderate sedation, allowing for sensory and motor block assessment. Patients were allowed spontaneous breathing with oxygen supplementation by nasal cannula. Glucose/saline solution was infused at a rate of 10 ml/kg/h. HR, mean arterial blood pressure (MAP), respiratory rate, and $SpO_2$ were monitored throughout the anaesthetic procedure.

The onset of sensory block was defined as the time from the moment of intrathecal injection of LA (time zero) to the moment of achievement of T10 sensory blockade. A skin pinch test was used to monitor the onset of the sensory block as it was advantageous compared to the usual pinprick test in being non-invasive, maintaining skin integrity and having the ability to be repeated

without discomfort,[6] Nevertheless, its efficacy is assured as mentioned by Mahdy *et al*.[7] Also, the maximum sensory block level was assessed every 2 min by a skin pinch test.

The onset of motor block is defined as the time from the moment of intrathecal injection of LA (time zero) to the moment of inability to flex ankle or move toes. Motor power was assessed using the modified Bromage scale, which scores the voluntary movement of leg and feet as follows: 0: no motor loss, 1: inability to flex the hip joint, 2: inability to flex the knee joint, but can flex the ankle and move the feet and 3: inability to flex the ankle or move the toes. Motor power was checked every 2 min till reaching a score of 3.[8]

HR and MAP were recorded immediately before the establishment of the spinal block (baseline), at the time of surgical incision, then every 15 min for 1 h and lastly at the end of the operation. PO monitoring included the efficacy of PO analgesia that was determined by an assistant who was blinded about the drugs used for intrathecal anaesthesia, using the observational pain–discomfort scale (OPS), which assesses behavioural parameters that can be evaluated objectively.[9] Each of the five variables of OPS, crying, facial expression, position of the torso, position of the legs and motor restlessness, was scored on a 3-point scale (1 = none, 2 = moderate and 3 = severe) to give a total score of 5–15, with 5 indicating excellent and 15 indicating ineffective analgesia. Rescue analgesia in the form of paracetamol suppository (15 mg/kg) was given at OPS >11 on two subsequent observations, 15 min apart, or if the patient had obvious signs of pain. Duration of analgesia, in minutes, was defined as the time elapsed since the end of the surgical procedure till OPS >11, and PO analgesia was given and repeated if necessary. PO resolution of motor block was assessed every 30 min till a Bromage score of 0 was attained, and this indicated complete motor recovery. The level of PO sedation was assessed at 30 and 120 min after admission to the recovery room using the modified Wilson Sedation Score (WSS), which is an objective scoring system evaluating sedation levels as asleep and not arousable by verbal contact (score = 4), asleep but arousable by verbal contact (score = 3), drowsy/not sleeping (score = 2) or alert/awake (score = 1), and so, the higher the score, the higher the level of sedation.[10] Patients were discharged home after they had regained full motor power and with a WSS of 1 or 2. Duration of PO hospital stay and frequency of anaesthetic procedure-induced complications or drug-related side effects were also recorded.

The primary outcome of the study was the efficacy of PO analgesia as judged by the severity of OPS score. The secondary outcome was the quality of intraoperative (IO) spinal anaesthesia that was defined as peak sensory level reached at least T10 and Bromage score of 3 at ≤10 min after spinal block with no response to surgical stimuli once the surgery was allowed to start. Cases that had failed spinal block received general anaesthesia and were excluded from statistical analysis.

The sample size was calculated according to the previous findings that the difference in PO duration of analgesia between midazolam and control groups was non-significant[11] when the sample size was 20 patients, so the sample size of the current study was decided to be tripled ($n$ = 60) to achieve a significant difference with the power of study of 80% and confidence interval (CI) of 95% and α value of 0.05. The obtained data were presented as mean, standard deviation (SD), median, interquartile range, numbers and percentages. Results were analysed using the one-way analysis of variance (ANOVA) test, Mann–Whitney test and Chi-square test ($\chi^2$ test) for comparisons between both groups. Statistical analysis was conducted using the International Business Machines Statistical Package for the Social Sciences (IBM SPSS) (version 23, 2015; IBM, Chicago, IL, USA) for Windows. $P$ value <0.05 was considered statistically significant.

## RESULTS

One-hundred and thirty-five patients were taken up for evaluation; 15 patients were excluded and 120 patients were randomly and equally divided into the study groups [Figure 1]. Statistically, patients' demographic data, distribution of the various types of operations and duration of surgery were comparable in both groups [Table 1].

Spinal block failure was not reported in both groups. The onset of sensory and motor block was significantly faster in group B/M than in group B/S ($P$ = 0.021 and 0.027, respectively).

The frequency of patients who had a Bromage score of 3 within ≤10 min was significantly ($P$ = 0.037) higher among patients of group B/M. The incidence

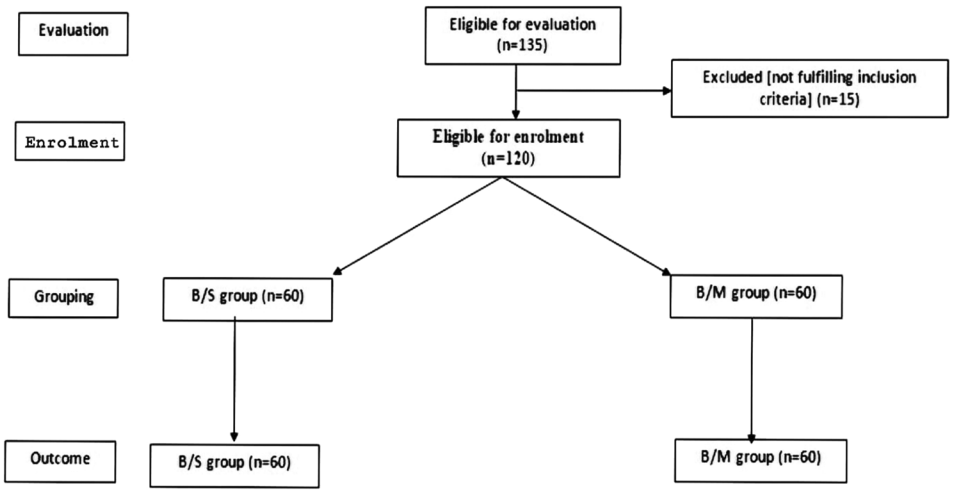


**Figure 1:** CONSORT flow chart. *n* = number of patients in each group. Group B/S included patients receiving intrathecal bupivacaine and saline; group B/M included patients receiving intrathecal bupivacaine and midazolam

**Table 1: Demographic and clinical data of patients of studied groups**

| Data | Group B/S | Group B/M | *P* |
|---|---|---|---|
| Age (years) | 7.9±2.5 | 8.1±2.2 | 0.638 |
| Weight (kg) | 25.9±6.7 | 28±5.5 | 0.062 |
| Gender | | | |
| Males, *n* (%) | 52 (86.7%) | 54 (90%) | 0.569 |
| Females, *n* (%) | 8 (13.7%) | 6 (10%) | |
| Indications for surgery | | | |
| Inguinal hernia | 32 (53.3%) | 29 (46.7%) | 0.556 |
| Undescended testis | 13 (21.7%) | 9 (15%) | |
| Cystolithotomy | 7 (11.7%) | 10 (16.6%) | |
| Cyst of round ligament | 3 (5%) | 7 (11.7%) | |
| Hypospadias | 5 (8.3%) | 6 (10%) | |
| Dose of bupivacaine | | | |
| <15 kg | | | |
| Number | 3 (5%) | 1 (1.7%) | |
| Total dose | 5.4 (0.5) | 5.2 | |
| >15 kg | | | |
| Number | 57 (95%) | 59 (98.3%) | |
| Total dose | 8 (1.8) | 8.5 (1.6) | |
| Total | | | |
| Total dose | 7.8 (1.9) | 8.4 (1.6) | 0.071 |
| Duration of surgery (min) | 71±14.7 | 67±15.6 | 0.151 |

*n*=number of patients in each group, *n* (%) = number and percentage of either males or females, SD=standard deviation. Group B/S included patients receiving intrathecal bupivacaine and saline; group B/M included patients receiving intrathecal bupivacaine and midazolam. Data were expressed as mean±SD, numbers and percentages (%). *P* value indicates the significance of difference between both groups; *P*<0.05 indicates significant difference; *P*>0.05 indicates non-significant difference

of sensory block level below T10, the number of patients who needed supplemental IO analgesia and the IO haemodynamic changes in both groups were comparable [Table 2]. Despite the non-significant differences between OPS and Bromage scores of the studied patients during the immediate PO follow-up period, time for regression of sensory and motor blocks were significantly longer in group B/M than in group B/S. However, the mean number of requests for PO analgesia was significantly lower by patients of the B/M group than patients of the B/S group. Moreover, the mean of WSS was significantly higher at 30 and 120 min PO in patients of group B/M in comparison to patients of group B/S. The mean duration of PO hospital stay was non-significantly longer in patients of group B/M in comparison to patients of group B/S. No procedure-related complications or drug-induced side effects were reported in all the study patients [Table 3].

## DISCUSSION

The obtained results concerning PO OPS scores and duration of PO analgesia go in hand with recent literature, which documents the efficacy of intrathecal anaesthesia.[12,13] Spinal anaesthesia in paediatrics is safe with fewer cardiorespiratory complications and has a rapid onset of action.[14]

Patients of group B/M who received midazolam as an adjuvant to LA showed significantly longer duration of PO analgesia with less consumption of PO analgesia in comparison to patients of group B/S who received LA only. These results illustrate the benefits of using adjuvant to LAs in order to get better outcomes, especially with regard to PO pain and spinal injection-induced complications. These results are in accordance with those of multiple studies that have tried various additives.[15-17]

Concerning midazolam as an adjuvant to LA, there is a paucity of clinical trials that have evaluated the efficacy of midazolam as an additive to nerve blocks because some earlier studies suggested

**Table 2: Intraoperative data of patients of studied groups**

| Data | Group B/S | Group B/M | *P* |
|---|---|---|---|
| Need to shift to general anaesthesia (*n*) | 0 | 0 | 0 |
| Duration of surgery (min) | 71±14.7 | 67±15.6 | 0.151 |
| Sensory block data | | | |
| Level | | | |
| Median (range) | 10 (7–10) | 10 (8-10) | 0.929 |
| <T10 | 5 (8.3%) | 2 (3.3%) | 0.464 |
| T10 | 55 (91.7%) | 58 (96.7%) | |
| Onset of sensory block (min) | 3.3±1.2* | 2.8±1* | 0.021 |
| Motor block data | | | |
| Time to reach score 3 on Bromage scale | | | |
| <10 min | 35 (58.3%)* | 45 (75%)* | 0.037 |
| 10 min | 8 (13.4%)* | 9 (15%)* | |
| >10 min | 17 (28.3%)* | 6 (10%)* | |
| Average (±SD) | 9.1±1.8* | 8±1.7* | 0.002 |
| Need for supplemental analgesia, *n* (%) | 3 (5%) | 2 (3.3%) | 0.648 |
| Haemodynamic data | | | |
| MAP (mmHg) | | | |
| Baseline | 62.3±4.7 | 61±5.6 | 0.164 |
| Incision | 63.9±4.5 | 62.1±5.5 | 0.051 |
| 15 min | 62.9±4.4 | 61.5±5.1 | 0.105 |
| 30 min | 62.5±4.1 | 61.5±5.3 | 0.212 |
| 45 min | 62.9±4.3 | 61.2±5.2 | 0.052 |
| 60 min | 62.7±4.2 | 61.3±4.8 | 0.129 |
| 75 min | 62.5±4.3 | 61.5±5.1 | 0.338 |
| 90 min | 62.4±4 | 61.7±5 | 0.647 |
| HR (beat/min) | | | |
| Baseline | 108.5±9.3 | 107.5±10.2 | 0.573 |
| Incision | 111.2±9.6 | 110.3±10.3 | 0.622 |
| 15 min | 106.9±9.2 | 105.8±10.3 | 0.552 |
| 30 min | 108.5±8.7 | 107.4±9.3 | 0.516 |
| 45 min | 107.8±9.5 | 106.3±10.4 | 0.425 |
| 60 min | 109.3±9.4 | 107.8±9.2 | 0.414 |
| 75 min | 108.9±9.4 | 108.9±9.4 | 0.976 |
| 90 min | 108.1±8.5 | 107.7±10 | 0.922 |

HR=heart rate, MAP=mean arterial blood pressure, *n*=number of patients in each group, *n* (%) = number and percentage of patients who needed supplemental analgesia, SD=standard deviation. Group B/S included patients receiving intrathecal bupivacaine and saline; group B/M included patients receiving intrathecal bupivacaine and midazolam. Data were expressed as mean±SD, numbers and percentages (%). *P* value indicates the significance of difference between both groups; *P*<0.05 indicates significant difference; *P*>0.05 indicates non-significant difference,*indicates significant difference

*in vitro* neurotoxicity of midazolam and its modest efficacy.[18,19] However, Dittmar *et al*.[20] examined the degree of apoptosis using an *in vitro* model that consisted of astrocyte-conditioned human umbilical vein endothelial cells using western blots and documented that midazolam did not significantly alter markers of apoptosis in comparison to control. Ulbrich *et al*.[21] experimentally assessed the mitochondrial membrane potential of injured neuronal cells and then exposed them to various LA additives, and they found that midazolam could not protect or aggravate these injured neurons.

Despite this controversy and debate, a review of literature defined multiple clinical trials in adults that used intrathecal midazolam and reported outcomes coincident with those of the current study, wherein Agrawal *et al*.[22] found that a combination of bupivacaine and midazolam intrathecally induced early onset of sensory blockade and prolonged duration of effective analgesia with decreased incidence of transient neurological symptoms. Also, Codero *et al*.[23] reported a significantly longer duration of effective analgesia and significantly lower pain scores with intrathecal midazolam than with intrathecal fentanyl, despite the significantly longer time to onset with midazolam.

Moreover, Basuni *et al*.[24] reported that combining low-dose intrathecal ketamine with midazolam and low-dose bupivacaine during spinal anaesthesia for caesarian section prolonged the analgesic duration

**Table 3: Postoperative data of patients of studied groups**

| Data | Group B/S | Group B/M | *P* |
|---|---|---|---|
| Sensory block data | | | |
| Duration of sensory block (min) | 221.6±59.2* | 247.8±56.9* | 0.015 |
| OPS score during PO follow-up (median; IQR) | | | |
| 30 min | 5 (5-5) | 5 (5-5) | 1 |
| 60 min | 5 (5-6.25) | 5 (5-6.25) | 0.757 |
| 90 min | 6.5 (6-8) | 6.5 (6-7) | 0.231 |
| 120 min | 8 (6-9) | 7 (6.75-8) | 0.177 |
| 150 min | 9 (8-10) | 8 (8-9) | 0.177 |
| 180 min | 9 (8-10) | 9 (8-10) | 0.803 |
| 210 min | 10 (9-12) | 10 (9-11.25) | 0.356 |
| 270 min | 10 (8-12) | 10 (8-12) | 0.391 |
| 330 min | 9 (8-12) | 8.5 (7-12) | 0.276 |
| PO analgesia | | | |
| Time of requests | 1.22±0.7* | 0.95±0.5* | 0.014 |
| Total dose (mg) | 1033.6±497 | 923.5±313.6 | 0.181 |
| Motor block data | | | |
| Duration of motor block (min) | 138.2±21.4* | 149.5±20.3* | 0.003 |
| Bromage score during PO follow-up (median, IQR) | | | |
| 30 min | 3 (3-3) | 3 (3-3) | 1 |
| 60 min | 2 (2-3) | 2.5 (2-3) | 0.158 |
| 90 min | 1 (1-2) | 2 (1-2) | 0.119 |
| 120 min | 1 (0-1) | 1 (0-2) | 0.258 |
| 150 min | 0 (0-1) | 0.5 (0-1) | 0.185 |
| 180 min | 0 (0-0) | 0 (0-0) | 1 |
| WSS | | | |
| 30 min | 2.55±0.9 | 2.88±0.7 | 0.024 |
| 120 min | 1.15±0.4 | 1.35±0.5 | 0.015 |
| PO hospital stay (h) | 215±45.9 | 229±43.5 | 0.089 |

IQR=interquartile range, OPS=observational pain–discomfort scale, PO=postoperative, WSS=Wilson Sedation Score. Group B/S included patients receiving intrathecal bupivacaine and saline; group B/M included patients receiving intrathecal bupivacaine and midazolam. Data are shown as mean, standard deviation, median, IQR. *P* value indicates the significance of difference between both groups; $P<0.05$ indicates significant difference; $P>0.05$ indicates non-significant difference, *Indicates significant difference

without significant adverse effects or any impact on the neonate. Intrathecal midazolam and ketamine have been previously found to be neurotoxic. Also, Sanwatsarkar *et al*.[25] showed that the addition of clonidine or midazolam to bupivacaine for caudal analgesia in children significantly increased the duration of PO analgesia with minimal side effects, in comparison to bupivacaine alone. Thereafter, Alam *et al*.[26] reported that intrathecal midazolam as an adjuvant to bupivacaine spinal anaesthesia did not affect the characteristics of the block, but significantly reduced pain scores, the requirement of IO analgesia and provided a significantly longer duration of PO analgesia. On the contrary, Sawhney *et al*.[27] and Amin *et al*.[28] reported significant improvement of anaesthetic and PO analgesia outcome of spinal anaesthesia when using combinations of bupivacaine and midazolam or fentanyl and with midazolam or nalbuphine in comparison to anaesthesia with bupivacaine alone, but with significant differences in case of using midazolam and either fentanyl or nalbuphine.[29]

The reported analgesic effect of intrathecal midazolam that was extended postoperatively to a significantly longer duration than bupivacaine alone could be attributed to the fact that midazolam causes segmental analgesia that is mediated by the benzodiazepine–GABA receptor complex, which is localised as a dense band within lamina II, especially inner lamina II of the dorsal horn, and with moderately high densities in laminae I and III.[29] As another explanation, Yilmaz-Rastoder *et al*.[30] attributed the prolonged analgesic effect of LA with midazolam as an adjuvant to the effect of midazolam on the compound action potentials from A- and C-fibres, as it attenuated both A- and C-wave amplitudes, but the attenuation was of greater potency on the C-wave.

This study was limited by the relatively small sample size, its single-centre design, relatively short time operations and usage of a fixed dose of midazolam (0.5 mg), which may not be the optimal dose. Therefore, wider-scale multicentre studies with a larger sample size should be conducted with different doses of midazolam and with longer time operations to identify the most appropriate midazolam dose and to prove or disprove the results of the present study.

## CONCLUSION

The addition of intrathecal midazolam to bupivacaine in children significantly improves the duration and quality of spinal anaesthesia and provides prolonged PO analgesia without significant side effects.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his/her consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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