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## Original Article

# Comparison of the onset and duration of analgesia with intrathecal hyperbaric bupivacaine and intrathecal hyperbaric bupivacaine plus midazolam for lower limb orthopaedic surgeries.

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**Abstract**

**Background:** Various additive drugs have been added to bupivacaine to modify its onset and duration of analgesia; these include among others the use of midazolam, tramadol, morphine and fentanyl. This study, therefore, was aimed at comparing the onset and duration of analgesia during intrathecal hyperbaric bupivacaine 0.5% alone and intrathecal hyperbaric bupivacaine 0.5% with midazolam for lower limb orthopaedic surgeries. **Methodology:** This was a prospective randomized double-blinded controlled study that recruited one hundred and thirty-eight (138) ASA I and II patients scheduled for elective lower limb orthopaedic surgeries. The patients were allocated into two groups. Group BA (n=69) received 12.5mg(2.5mls) of 0.5% hyperbaric bupivacaine with 0.5mls normal saline intrathecally at L3-L4 or L4-L5 inter-space, and group BM that received 12.5mg (2.5mls) of 0.5% hyperbaric bupivacaine with 2.5mg (0.5mls) of preservatives-free midazolam at L3-L4 or L4-L5 intrathecally, no premedicants were given. Standard monitoring of the vital signs was done. The onset and duration of analgesia were documented and analysed. **Results:** Results showed that the mean onset time of analgesia was 37.04±4.53min and 25.65±4.84min in groups BA and BM respectively, with statistically significant difference ($P < 0.01$). While the mean duration of analgesia were151.43 ± 58.84 min and 323.4 ± 22.55 min in groups BA and BM respectively, $P<0.01$. **Conclusion:** The addition of 2.5mg (0.5ml) of midazolam to hyperbaric bupivacaine for subarachnoid block shortens the onset and prolonged the duration of analgesia when compared to bupivacaine alone.

**Keywords:** *Analgesia, Bupivacaine, Duration of action, Midazolam, Onset of action*

## Introduction

Spinal anaesthesia, otherwise known as subarachnoid or intrathecal block, is a reliable and established technique of providing anaesthesia for lower abdominal and lower limb surgeries.1Intrathecal block is simpler, cheaper and safer than it used to be in the past.2,3 Reasons may be attributed partly to more standardized doses of the drugs(local anaesthetics), improved skill and management of complications promptly.4

Spinal anaesthesia is usually indicated for infra-umbilical surgical procedures and lumbar spine e.g. caesarean deliveries, lower limb orthopaedic surgeries (amputations, open reduction and internal fixation etc.), urological procedures (prostatectomy, urethroplasty), and general surgeries (appendectomy, fistulotomy/fistulectomy, herniorrhaphy).5

Pain management is a Human Right, necessary based on humanitarian grounds as well as for therapeutic reasons; however, failure to relieve pain may lead to tachycardia, hypertension, hypoxia, restlessness, nausea and vomiting, increase in metabolism and sleep disturbances in the patient.6

Also, effective acute pain management is likely to

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improve the quality of clinical care by preventing complications, reducing hospital stays and promoting recovery and rehabilitation. Pain from surgical stimulation tends to be acute and severe when the means of achieving adequate analgesia is not adequately planned or given to the patient. Pain in a surgical patient tends to be underestimated by the Surgeon and Anaesthetist. [5]

Limitations associated with spinal anaesthesia using local anaesthetics alone include short duration of action and side-effects of local anaesthetics like profound hypotension. However, spinal anaesthesia using a local anaesthetic agent in combination with additives is one of the methods employed to manage acute intraoperative and postoperative pain. 7 Studies have shown the effectiveness of opioids as an adjunct to bupivacaine for spinal anaesthesia but the use of benzodiazepines has not been explored extensively. [6]

Midazolam one of the commonly use benzodiazepines in anaesthesia produces antinociception and potentiates the effect of local anaesthetic when administered intrathecally, without having significant unwanted effects. 8 Intrathecal 2.5mg midazolam was chosen because of the minimal adverse effects associated with its use as demonstrated by a large prospective cohort study.[8]
This study, therefore, was aimed at evaluating the onset and duration of analgesia following intrathecal 0.5% hyperbaric bupivacaine alone with intrathecal 0.5% hyperbaric bupivacaine with 2.5mg midazolam as an additive in lower limb orthopaedic surgeries.

**Materials and Method**

The study was a prospective, double-blinded, controlled, randomized clinical trial in patients who were scheduled for elective lower limb orthopaedic surgeries between the ages of 18-60 years of American Society of Anaesthesiologists (ASA) classification I and II, for six (6) months at University of Maiduguri Teaching Hospital, Maiduguri, Borno state, Nigeria.

The study was conducted at the Department of Anaesthesia, University of Maiduguri Teaching Hospital, Maiduguri, Borno state, Nigeria, following approval by the ethical committee of the hospital.

Data was collected from 138 patients that undergone lower limb orthopaedic surgeries under spinal anaesthesia. Both study and control groups were selected from these patients.

The inclusion criteria included all patients that consented to the research, ASA I and ASA II patients, ages of 18-60 years, both sexes and elective lower limb orthopaedic surgeries, while the exclusion Criteria included the patient refusal, ASA above II, ages less than 18 years and above 60 years, coagulopathy, severe hypovolaemia, skin/soft tissue infection at the site of injection, increased intracranial pressure, pre-existing neurologic disease, the inability of a patient to maintain stillness, emergencies and failed spinal anaesthesia.
All eligible patients were visited a day before surgery for pre-operative review.

A history of drug allergy and blood transfusion were obtained. No premedication was prescribed. Each patient was fasted for six hours from solid food before the surgery.

On the morning of the surgery, a routine Anaesthetic machine check was done, and the necessary resuscitation drugs were made available. The Patient's peripheral vein was cannulated with a wide-bore intravenous cannula size 16 G or 18 G. The demographic data (age, weight, gender and height) of the patient were taken and the body mass index (BMI) was calculated as Weight (kg)/Height ($m^2$).

Multi-parameters monitors were attached to the patient and baseline vital signs were obtained and documented which included non-invasive blood Pressure (NIBP), mean arterial pressure (MAP), Heart rate (HR), Respiratory rate (RR), Electrocardiogram (ECG) and arterial oxygen saturation ($SpO_2$) using 'Drager infinity gamma XL multi-parameters Patient monitor'. All patients were preloaded with crystalloids (0.9% saline or lactated Ringer's solution) 10 ml/kg body weight over 20 min before spinal injection. Subsequently, fluid was administered at a maintenance dose of 15 ml/kg/hr intra-operatively.

Randomization of patients was achieved by balloting. Pieces of paper numbered 1-69 for group BA, and 1-69 for group BM were put in a small opaque envelope and sealed. The envelopes were

put in a basket. After thoroughly shaking and turning over the basket to the trained assistant at the theatre reception, each patient was asked to pick one envelope and handed it over to the trained assistant.
The trained research assistant (assistant 1: anaesthesia resident with at least 2 years of experience, who had not performed subarachnoid block or recorded the outcome of the intraoperative and postoperative period), who was trained in preparing the drug under aseptic conditions according to the group on the piece of paper inside the envelope using codes known to him alone and using 5 ml syringes of the same brand for all groups and maintaining same volume level of all drug samples. The researcher administered the drug that was blinded to both the content of the envelope and the drug preparation. Another trained research assistant (assistant 2: anaesthesia resident) records in the proforma. Both the investigator (performing the study) and the patient were blinded to the content of the drugs contained in the syringes.

The procedures were done under aseptic conditions. The skin, subcutaneous tissue, supraspinous and interspinous ligaments were infiltrated with 2 ml of 1% plain lidocaine. A spinal needle size 25G Quincke type was inserted at L3/L4 or L4/L5 vertebral interspace. After obtaining a free flow of cerebrospinal fluid, the study drugs (bupivacaine and midazolam for the BM group and bupivacaine alone for the BA group) had been administered into the subarachnoid space over 20 seconds without barbotage. The spinal needle was then removed and sterile gauze was was applied to the site of injection and adhesive plaster was applied. After injection, the patient was positioned supine. The end of the spinal injection was taken as time zero minute.

Observation and assessments of sensory level were made. The arterial blood pressure (systolic, diastolic and mean), respiratory rate, electrocardiogram and arterial oxygen saturation using a pulse oximeter were recorded in the following sequence-every minute for the first five minutes, thereafter every five minutes until the end of surgery.

The sensation was tested along the midaxillary line using a pin-prick at 3, 5, 10, and 15 minutes following spinal injection, at the end of the surgery, and before giving postoperative analgesia to the patient.

The patient was withdrawn from the study if the spinal block failed or the patient decided to withdraw his/her consent to participate. A Standard questionnaire was used to document the demographic characteristics of the patients and the onset and duration of spinal analgesia.
The data were analysed by the use of Epi info version 3.5.3 statistical software (2011). Numerical data were analysed using the student's t-test and categorical data was analysed with the chi-square test. $P< 0.05$ was considered statistically significant.

**Results**

A total of one hundred and thirty-eight (138) ASA I and II patients between the ages of 18-60 years were recruited in both of the groups consisting of 37 (54%) males and 32 (46%) females (M: F 1.2:1) in hyperbaric bupivacaine alone group, while in hyperbaric bupivacaine-midazolam group, 36 (52%) were males and 33 (48%) females (M: F 1.1:1). There was 1 (1.5%) patient in hyperbaric bupivacaine alone group (BA) and 4 (5.8%) patients in hyperbaric bupivacaine-midazolam group (BM) who had failed block and were converted to general anaesthesia and they were excluded from the study.
There were no statistically significant differences with regard to the age, gender, weight, height, body mass index (BMI), and ASA classification between the two groups as shown in Table 1.

The mean onset time of analgesia was 37.04±4.53 min and 25.65±4.84 min in groups BA and BM respectively, and the difference was statistically significant ($p<0.01$), as shown in Table 2. The mean duration of analgesia was 151.43 ± 58.84 min and 323.4 ± 22.55 min in groups BA and BM respectively, with a statistically significant difference ($p <0.01$) as represented in Table II.

**Table 1: Socio-demographic data of the patients in groups A and B**

| Variable | BA | BM | p-value |
|---|---|---|---|
| Age ( Mean SD) (year ) | 41.23 ±12.78 | 37.07 ±13.60 | 0.07 |
| Gender | | | |
| Male n (%) | 37 (51) | 36 (49) | 0.87 |
| Femal e n (%) | 32 (49) | 33 (51) | |
| Weigh t (Mean±SD) (kg) | 68.69±14.82 | 66.57±13.47 | 0.38 |
| Height (Mean ±SD) (m) | 1.68 ± 0.08 | 1.67 ± 0.08 | 0.58 |
| BMI (Mean± SD) (kg/m²) | 26.73 ± 17.66 | 24.02 ± 4.69 | 0.22 |
| ASA Class | | | 0.14 |
| I n (%) | 17(40%) | 25(60%) | |
| II n (%) | 52(54%) | 44(46%) | |

**Table 2: Onset and duration of analgesia in group BA and BM**

| Variables | BA | BM | P-value |
|---|---|---|---|
| Onset of analgesia (Mean ±SD) (min) | 37.04 ± 4.53 | 25.65 ± 4.84 | 0.01 |
| Duration of analgesia (Mean ±SD) (min) | 151.43 ±58.84 | 323.4 ± 22.55 | <0.01 |
| Conversion to general analgesia n (%) | 1(1.5) | 4(5.8) | 0.17 |

## Discussion

In the present study, the shorter mean onset of action of analgesia in the bupivacaine and midazolam group (25.65 ± 4.84 min) was compared to the bupivacaine group only (37.04 ± 4.53 min) and was found to be statistically significant, this was similar to the findings by Braga et al,11 where they found that the onset of the blockade was significantly faster in groups with adjuvant (midazolam) compared with Group I (no adjuvant). This shows that the addition of midazolam to bupivacaine for intrathecal anaesthesia tends to shorten the mean onset of action of analgesia compared to bupivacaine alone. The reason for this similarity may not be far-fetched as they equally used the same drugs as in this study.

In the present study, the mean duration of analgesia was statistically significant between the two groups BA and BM with 151.43 ± 58.84 min and 323.4 ± 22.55 min respectively, the duration of analgesia was prolonged by 172 min in group BM compared to BA alone group (i.e., 323 min in BM group as against 151 min in group BA). This represents a period of prolongation of postoperative analgesia; possibly due to the residual analgesic effect of midazolam that became manifest after the sensory block with bupivacaine had been dissipated, the findings were not comparable. This was supported by previous pre-clinical studies which demonstrated the potential role of spinal benzodiazepine receptors in the segmental anti-nociceptive action of intrathecal midazolam.12,13

Goodchild et al, 14 conducted a similar clinical trial in humans earlier. These findings were similar to the result obtained by Kim et al, 15 where they found a statistically significant difference between the use of bupivacaine and midazolam compared to bupivacaine alone for spinal anaesthesia also studies by Aikta et al,–16 and Chattopadhyay et al,17 shows similar results. This similarity may not be unconnected with the use of a similar agent (midazolam) in the intrathecal space as an additive to hyperbaric bupivacaine for infraumbilical surgeries as in the present study. The addition of midazolam 2.5 mg intrathecally prolonged the duration of spinal analgesia to 5.4 hr in our study. Similarly, in the study by Kim et al,15 they also reported that, in a meta-analysis, the addition of 1mg or 2 mg of intrathecal midazolam prolonged the postoperative analgesic effect of bupivacaine by 2 hr and 4.5 hr, respectively, as compared to the control group after hemorrhoidectomy, and this finding suggested a dose-dependent action of intrathecal midazolam.

It was reported that hemorrhoidectomy pain can be alleviated only by sacral sensory nerves. In the present study, the patients had lower limb orthopaedic surgeries; therefore, for effective analgesia to be achieved there is a need to block the lower lumbar dermatomes as well.

Furthermore, in the study by Batra et al,22 they reported an increased duration of postoperative pain-free with intrathecal midazolam 2 mg and bupivacaine in 30 patients that had knee arthroscopy, all patients received rescue analgesia in the control group at a mean duration of 258 ±46.8 min whereas only one patient in midazolam bupivacaine group required supplemental analgesia within this period. Intrathecal midazolam 2 mg provided a moderate prolongation of postoperative analgesia when used as an adjunct to bupivacaine in patients that had caesarean deliveries.23 Similar corroborative results were obtained in a study conducted by Prakash et al, 23 that assessed the postoperative analgesic efficacy in patients that had an elective caesarean section. They reported 6.1 hours in the prolongation of postoperative analgesia. They reported more prolonged postoperative analgesia compared to this study the reason may be because of the different types of surgery used.

Also, Kim and Lee, 24 similarly reported 4.5 hr of postoperative analgesia in patients who had haemorrhoidectomy with the addition of 2 mg intrathecal midazolam to bupivacaine for spinal anaesthesia this is lower than in this present study, the possible reason for the lower duration is because of haemorrhoidectomy is a more painful procedure compared to this present study. The higher sensory block level with more caudal wound incisions (anal region versus lower limb orthopaedic surgeries) also explains the difference.

However, our study differs from those of Batra et al, 22 and Sidiq et al, 25 who also used 2 mg preservative-free intrathecal midazolam added to bupivacaine. However, in the work of Batra and colleagues, 22 they used it for knee arthroscopy which duration of surgery was relatively shorter than other lower limb orthopaedic surgeries. In addition, the rate of sensory regression which may correlate with the duration of postoperative analgesia is rather slow in lower limb orthopaedic procedures. The skeletal component of pain predominates in motor innervations in orthopaedics, which is 1-2 segments lower than that of sensory innervations. In addition, the L5-S2 segments that sub-serve the lower limb remain blocked for the longest period.26

In addition, the variable results include the potency of midazolam and bupivacaine used, the effects of storage on the study drugs, and genetic predisposition may have accounted for the prolonged effects seen in this study. Also, the nature and types of gynaecological procedures studied by Sidiq et al, 25 were not defined. Thus, leaving a vacuum on the assumed duration of surgery and grouping of procedures involving widely separated dermatomes. The 2 mg midazolam administered in their study is against the 2.5 mg midazolam used in the present study and this favours the dose-dependent principles with midazolam (i.e., the indifference may be dose-related). From the available literature, 22,27 surgical cases limited to the lower extremity reported more prolonged postoperative analgesia as the rate of 2-segment regression was slower in these cases. It is difficult therefore to compare sensory block regression which determines the duration of analgesia in myomectomy to that in perianal surgeries and lower limb orthopaedic procedures.

**Conclusion**

The addition of 2.5mg (0.5ml) of midazolam to hyperbaric bupivacaine for subarachnoid block shortens the onset and prolonged the duration of analgesia when compared to bupivacaine alone.

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