Comparative Study of Intrathecal Midazolam Used as Adjuvant to Intrathecal Bupivacaine with Intrathecal Bupivacaine Alone in Orthopedic Surgeries

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Abstract

Background: Spinal anesthesia is a common technique used in orthopedic surgeries involving hip and lower limbs. It provides adequate analgesia both intra and post-operative and it also avoids complications associated with general anesthesia.

Spinal block remains the first choice in these kinds of surgeries due to its rapid onset, superior blockade, less failure rates and cost effectiveness, but has the drawbacks of shorter duration of block and lack of postoperative analgesia.

Use of intrathecal adjuvants has gained popularity with the aim of prolonging the duration of block, better success rate and patient satisfaction.

Methods: 60 patients, ASA I/II were enrolled into the study. All patients had spinal anesthesia and randomly allocated into one of two groups. Group C: (30 patients): The patient received 15mg of bupivacaine 0.5% plus 0.4ml saline, Group M: (30 patients): The patient received 15mg of bupivacaine 0.5% plus 0.4ml of midazolam (2mg). In both groups assessment was done for time to reach T10 dermatome, time to peak sensory level, time to reach complete motor block (Bromage 3), regression to S1 dermatome and time for motor recovery.

Results: This study demonstrated that the Midazolam group was associated with increased sensory block time with no increase neither in onset nor in motor block duration. Hemodynamic variables were stable and there were no significant differences between both groups.

Conclusion: Finally, it is concluded that Midazolam (2mg) is effective as useful adjuvant to Bupivacaine for intrathecal anesthesia. Midazolam increased the duration of sensory block but with less duration of motor block. Midazolam also reduced intraoperative shivering with no significant side effects.

Key Words: Spinal anesthesia – Adjuvants – Bupivacaine and Midazolam.

Introduction

In recent years, use of intrathecal adjuvants has gained popularity with the aim of prolonging the duration of spinal block and to increase the success rate, patient satisfaction, decreased resource utilization compared with general anesthesia and faster recovery. Adequate pain management is essential to facilitate rehabilitation and accelerate functional recovery, enabling patients to return to their normal activity more quickly. The quality of spinal anesthesia has been reported to be improved by the addition of opioids (such as morphine and fentanyl) and other drugs [such as Dexmedetomidine (DXM), clonidine, magnesium sulfate, neostigmine, ketamine and midazolam] [1].

Benzodiazepines are used primarily for anxiolysis, amnesia and sedation. However, recent investigations have shown that some forms of this group of drugs have also direct effect on pain. Some investigators have suggested that spinal cord benzodiazepine receptors can play an important role in producing sufficient analgesia. It has further been argued that intrathecal midazolam reduces excitatory GABA-mediated neurotransmission in interneurons, leading to a decrease in the excitability of spinal dorsal horn neurons. Intrathecal-administered midazolam when added to bupivacaine significantly improved the duration and quality of spinal anesthesia; produced a more effective and longer analgesia in perianal and lower extremity surgeries; prolonged the duration of spinal blockade in orthopedic patients, and provided postoperative early recovery of motor function in orthopedic patients; in majority of these studies, no serious adverse effects were reported [2,3].
Aim of the Work:

This prospective randomized controlled study is conducted to evaluate the onset and duration of sensory and motor block as well as perioperative analgesia, adverse effects and effectiveness of Midazolam given intrathecally with 0.5% hyperbaric bupivacaine for spinal anesthesia.

Patients and Methods

The present study was a prospective randomized blind controlled study conducted for patients scheduled to undergo elective lower limb orthopedic surgeries under spinal anesthesia in Kasr Al-Aini Hospital, Cairo University during 2014. After obtaining Institutional Ethics Committee approval and written informed consent, 60 patients ASA I/II were enrolled into the study.

Inclusion criteria: ASA I, II patients, aged 18-45 years old, height 160-190 cm, weight 50-90 kg., Scheduled for lower limb surgery (knee arthroscopy, Tibial fractures, Femur fractures, etc...).

Exclusion criteria: Any contraindication to spinal anesthesia (patient refusal, severe cardiac disease, severe labile hypertension, raised intracranial pressure or pre-existing neurological disorders, such as multiple sclerosis), patients with coagulopathy due to liver or blood disease, therapeutic anti-coagulation, inability to communicate and understand the aim of the project, patients with history of allergic reaction to local anesthetics or benzodiazepines, skin infection at injection site or systemic bacteremia and failure of the block and need for general anesthesia.

Preoperatively the following routine investigations were done for all patients:

Complete Blood Count (CBC), blood grouping, Coagulation profile: Prothrombin Time (PT), Prothrombin Concentration (PC), Partial Thromboplastin Time (PTT), International Normalized Ratio (INR), Bleeding Time (BT), Clotting Time (CT), Random Blood Sugar (RBS), blood urea, serum creatinine, Alanine Aminotransferase (ALT), Aspartate aminotransferase (AST), blood Albumin, bilirubin total and direct, Electrocardiogram (ECG) for patients aged >40 years, X-ray chest, serum electrolytes if necessary.

Anesthetic procedure:

Upon arrival to the operating theatre, venous access was secured using an 18G venous cannula with no premedication given. Measurements of baseline hemodynamic parameters were recorded.

All patients were monitored intra-operatively using: An ECG, non-invasive blood pressure, and pulse oximetry. An infusion of Ringer’s lactate solution was started as a bolus of 500ml in 15min. All patients had spinal anesthesia; patients were put in sitting position. Under strict aseptic precautions, the back was sterilized using povidone iodine at the site of insertion, tips of lumbar spine were palpated and L3-4 space was selected. The skin was infiltrated with about 2ml of 1% lignocaine. Lumbar puncture was performed at the L3-L4 level through a midline approach using a 25G spinal needle.

Using closed envelopes random numbers, patients were allocated into two groups:

Group C (control group): (30 patients): The patient received 15mg hyperbaric bupivacaine and 0.4ml normal saline as control.

Group M (midazolam group): (30 patients): The patient received 15mg hyperbaric bupivacaine and 0.4ml (2mg) midazolam (Dormicum® by Roche).

After intrathecal injection, patients were positioned in supine position and oxygen 4L/min was given through a face mask. The anesthesiologist performing the block didn't know the study drug used and recorded the intraoperative data. Sensory block was assessed bilaterally by using loss of sensation to cold with alcohol gauze in the mid-clavicular line.

Motor blockade was assessed by using the modified Bromage scale:

Bromage 0, the patient is able to move the hip, knee and ankle.

Bromage 1, the patient is unable to move the hip but is able to move the knee and ankle.

Bromage 2, the patient is unable to move the hip and knee but able to move the ankle.

Bromage 3, the patient is unable to move the hip, knee and ankle.

Data collected: We measured the time to reach T 10 dermatome sensory block, time to reach peak sensory block level, time to reach Bromage 3 motor block was recorded, the recovery time from sensory and motor block were recorded in a Post Anesthesia Care Unit (PACU).

Sedation: Was assessed using modified Ramsay sedation score:

Grade 1: Anxious, agitated and restless.

Grade 2: Cooperative, oriented and tranquil.
Grade 3: Responds to commands only.

Grade 4: Brisk response to light glabellar tap or loud noise.

Grade 5: Sluggish response to light glabellar tap or loud noise.

Grade 6: No response.

**Vital signs:** Blood pressure AND heart rate

[Hypotension (defined as a decrease of more than 30% from the baseline mean arterial blood pressure (MAP), or systolic blood pressure less than 90 mmHg and bradycardia (defined as a heart rate <60bpm). Hypotension will be managed with an IV bolus of 250ml of crystalloids and if severe, 9-12mg of ephedrine will be given. Bradycardia will be managed with atropine 0.5mg IV. Patients were also evaluated for the presence of nausea and vomiting.

**Results**

**Demographic data:** Sixty patients were enrolled in the study. All of them were male patients with a mean age of 32.3±6.5 years; average duration of surgery was about one hour in all groups. There was no statistical difference between the groups as regard age, body mass index, duration of surgeries that included knee arthroscopy, Tibial fractures, Pott's fractures and femur fractures.

**Characteristics of the block:**

- **Onset to T10 dermatome:** There was no statistical significance between the midazolam group (2.95 minutes ±1.14) when compared to the control group (2.92 minutes ±0.93) regarding onset of the block ($p$-value >0.05).

- **Time to peak sensory level:** There was no statistical significance between the midazolam group (5min. ±1.51) when compared to the control group (5.52min. ±1.39), in the time needed to reach peak sensory level. ($p$-value >0.05).

- **Time to reach Bromage 3 motor block:** There was no statistical significance between the midazolam group (4.46min. ±1.53) when compared to the control group (4.72min. ±1.82) ($p$-value >0.05).

- **Regression to S1 dermatome:** The time passed for regression to S1 was more prolonged in patients of the midazolam group (217min. ±32) when compared to the control group (179min. ±19). This difference was statistically significant ($p$-value <0.01).

- **Recovery of motor power:** There was no statistically significant differences when comparing midazolam group (188min. ±29) to the control group (175min. ±18). ($p$-value >0.05).

Comparing systolic and diastolic arterial blood pressures in the intra-operative period revealed statistically significant lower systolic and diastolic pressures in each group at the 10 minutes reading compared to its baseline values, however there were no statistically significant differences observed while comparing the two study groups with each other. Also there were no significant changes in each group at the successive readings compared to their baseline values. Regarding heart rate, Comparing in the intra-operative period revealed statistically significant bradycardia in each group at the 20 minutes reading when compared to its baseline values, however there were no statistically significant differences observed while comparing the two study groups with each other. Regarding side effects, there was a remarkable statistically significant decrease in shivering when comparing the control group (56.7%) with the Midazolam group (26.7%) ($p$-value <0.05).

There was no statistical difference between the two groups as regarding other side effects like nausea, vomiting, pruritus, and headache.

**Discussion**

In this study we tried to compare the adjuvant effect of adding midazolam to bupivacaine in orthopedic surgeries in adults.

Each group consisted of 30 patients, randomly allocated for bupivacaine (15mg) alone as control, and bupivacaine (15mg) plus midazolam (2mg).

When comparing the demographic data in the two groups involved in the study, in respect to age, body mass index, duration of surgery and gender, there were no statistically significant differences observed between the study groups.

For estimation of the onset of the block we recorded three measurements, which are the time for the anesthetic to reach T 10 sensory level, time to reach the peak sensory level and time to reach Bromage grade 3 (G3). As regard the onset of the block, we found that this was achieved with small but not statistically significant difference in the midazolam group. For estimation of duration of block, we measured the time taken to regression of sensory level to S 1 dermatome and regression of motor block to Bromage grade zero. We found that the time passed for regression to S 1 was more
prolonged in patients of the midazolam group when compared to the control group (p-value <0.01). This difference was statistically significant. We also assessed the degree of sedation by using modified Ramsay sedation score, but we found no difference in sedation degree.

When comparing the results of the addition of midazolam adjuvant to other studies, Shadangi et al., [4] studied 100 patient for the effect of intrathecal midazolam compared to placebo, and Ho et al., [8] conducted a meta-analysis on 13 randomized control studies from Medline, Embase and Cochrane databases dated till end of 2007, involving 672 patients. Both studies had the same conclusion, that intrathecal midazolam improves perioperative analgesia without increase in duration of motor block with reduction in post-operative nausea and vomiting. These results agree with this study except when comparing nausea and vomiting.

Chattopadhyay et al., [6] and Safari et al., [7] are recent studies that compared intrathecal bupivacaine to intrathecal bupivacaine and midazolam in elective surgeries. They found similar results as regards the effect of these adjuvants on prolongation of analgesia time. In addition there was an increase in motor block that was significant. Chattopadhyay et al., [6] found decrease incidence of nausea and vomiting with midazolam.

Contrary to our study, Karbasfrushan et al., [2] compared intrathecal midazolam to placebo as an adjuvant to bupivacaine in 112 case undergoing cesarean section, they found no difference in time of effective analgesia and time of sensory regression, not only that, but they also noticed increased sedation in midazolam group with decrease incidence of nausea and vomiting in midazolam group.

Although they used the same dose of midazolam used in this study (2mg), the bupivacaine dose used was different (10mg vs. 15mg). The difference in bupivacaine dose, demographic data (gender, type of surgery, and age), and the difference in sample size (60 vs. 112), may be the reason for these controversial results.

Limitations of this study included, difficulty to standardize the pain variable as it is a subjective phenomenon associated with a wide variability of responses among the individuals. What may be tolerable for one person may be intolerable for another. Under these circumstances it is difficult to assess and grade the pain in the same manner which can lead to a lot of unwanted bias.

Difference in type of surgery may also lead to variations in duration of analgesia, as endoscopic surgeries are less painful than open surgical techniques. This can be negated in future studies by selecting similar type of patients undergoing same operative procedure.

We didn't focus on post-operative side effects as post-operative nausea and vomiting, we only observed intraoperative side effect and that may give under estimation of adjuvants role in preventing post-operative complications.

Our used dose of midazolam (2mg) is based on average doses used in previous literature, more studies should be done to compare different doses of the same drug to identify the appropriate dose for intrathecal route.

**Conclusion:**

Finally, it is concluded that Midazolam (2mg) is effective as a useful adjuvant to the local anaesthetic for intrathecal anesthesia. Midazolam increase the duration of sensory block but with less duration of motor block and reduce intraoperative shivering with no significant side effects.

**References**


التخدير التسنيفي هو أسلوب شائع جدا مستخدم في عمليات العظام التي تخص الفخذ والأطراف السفلية. ويوفر تسكين كافى للآلام أثناء وبعد الجراحة على حد سواء. ويتوجب أيضا الملاحظة المرتبطة بالتخدير الكلى. إن استخدام المواد المساعدة أكتسب شعبية بهدف إطالة المدة، وتحسين معدل النجاح، وإرضاء المرضى. هناك العديد من الدراسات التي تستخدم الميدازولام باعتباره أحد المواد المساعدة للبيوفيكسين.

أجريت هذه الدراسة لتقييم العقار من حيث سرعة بداية التخدير ومدى إطالة مدة ودائع تسليك الألم المحلي بالجراحة. ومقارنة الأثار السلبية وفعالية الميدازولام كعامل مساعد للبيوفيكسين في التخدير التسنيفي وقد أظهرت نتائج هذه الدراسة أن هذا العقار يفيد عند إضافته إلى عقار البيوفيكسين حيث أن الميدازولام يقام بإطالة مدة عمل المخدر وقوته، وأنه لجدير بالذكر أنه لم يتم ملاحظة أعراض جانبية لهذه العقار.

أثناء الدراسة الحالية.