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RESEARCH ARTICLE

Effect of Midazolam and 0.5% Levobupivacaine Combination in Ultrasound-guided Supraclavicular Brachial Plexus Block for Upper Limb Surgeries - A Clinical Study

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Abstract:

Background:

The present study was designed to evaluate the hypothesis that midazolam as an adjuvant to levobupivacaine would safely enhance the duration of analgesia without any adverse effects when compared with levobupivacaine alone, in ultrasound-guided supraclavicular brachial plexus block. Primary end points were the duration of sensory and motor block and secondary end points were sedation score and any other complications.

Patients and Method:

Eighty consenting patients of both sexes, aged 18-60 years of ASA physical status I-II were randomized into two groups of 40 patients each. Patients in Group LS received 19 ml of 0.5% levobupivacaine with 1 ml normal saline and patients in Group LM received 19 ml of 0.5% levobupivacaine with 1ml midazolam (50µg/kg) for supraclavicular brachial plexus block using ultrasound guidance. Onset time and duration of sensory and motor blockade and VAS scores were assessed as primary end points. Hemodynamic changes, sedation or any other drug or technique related adverse effects were taken as secondary effects.

Results:

Onset of sensory and motor blockade was lower in patients of Group LM. The mean duration of sensory analgesia was significantly prolonged in patients of Group LM (537.6 ± 101.01 *vs*. 319.80 ± 87.09 mins). The mean duration of motor blockade was also significantly enhanced in patients of Group LM (405.0 ± 61.62 mins) compared to Group LS (274.8 ± 46.30 mins). VAS scores were higher in Group LS than group LM. Sedation scores were similar in both the groups.

Conclusion:

Midazolam with 0.5% levobupivacaine has effectively enhanced the duration of sensory and motor block without significant sedation and any other side effect.

Keywords: Brachial plexus block, Levobupivacaine, Midazolam, Ultrasound guidance.

INTRODUCTION

Levobupivacaine is a relatively new long-acting local anaesthetic, with a pharmacological activity very similar to

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that of racemic bupivacaine [1]. Enthusiasm for levobupivacaine use has emerged after a few instances of extreme cardiotoxicity of the D-isomer of bupivacaine, which showed its higher potential for toxicity [2, 3]. Similar clinical activity and better tolerability with less cardiac and neurotoxicity make levobupivacaine, a better choice than racemic bupivacaine [4].

In quest of enhancing the quality and duration of the block, over the years, many adjuvants have been investigated with local anaesthetics. The continuous search for the new alternative drug is still going on since every drug has its benefits and side effects. Midazolam, a water soluble, short acting benzodiazepine, is known to produce antinociception thereby enhances the effect of local anaesthetic when used as an adjuvant to central neuraxial block. This effect of midazolam is due to its action on Gamma Amino Butyric Acid–A (GABA-A) receptors. Extrasynaptic receptors for GABA are present on myelinated axons of peripheral nerves, where midazolam acts to produce analgesia when used with local anaesthetic for peripheral regional blocks [5, 6]. The relatively low cost of midazolam is an additional benefit.

The present prospective randomized double-blind control study was planned to assess the clinical efficacy of midazolam as an adjuvant to 0.5% levobupivacaine for ultrasound-guided supraclavicular brachial plexus block.

Objectives of this study,

Primary endpoints:

1. To compare duration of sensory block (analgesia) between the two groups
2. To compare duration of motor block between the two groups

Secondary endpoints:

1. To compare level of sedation and any other complication in the two groups

MATERIAL AND METHODS

After approval from the Institutional Ethical Committee and written informed consent from all the patients, 80 adult patients of both sexes, aged between 18-60 years, of ASA physical status I and II, scheduled for elective unilateral below shoulder surgeries, under ultrasound-guided supraclavicular brachial plexus block were included in this prospective randomized double-blind study. Exclusion criteria included the following: coagulopathy, history of brachial plexus injury, allergy to the study drug, patients on chronic opioid use, seizure disorder, hepatic or renal insufficiency, significant cardiorespiratory disease, peripheral neuropathy, psychiatric patients, patient refusal and infection at the site of injection.

Sample Size Estimation

The preliminary sample size was decided in consultation with a statistician. It was calculated that at least 35 patients were necessary for each group to detect 20% increase in duration of analgesia after addition of midazolam with type 1 error (alpha) of 0.05 and type 2 error (beta) of 0.80 with 95% confidence limit. Assuming a 10% dropout rate, the final sample size was set at 40 patients in each group *i.e*. 80 patients in total.

Randomization and Blinding

Randomization was done by card method. A total of 80 cards were prepared by another anesthesiologist who was blinded about the study and after recruitment, every patient was allowed to draw one card and grouped accordingly into two equal groups of 40 patients each. Patients in Group LS received 19 ml of 0.5% levobupivacaine with 1 ml normal saline and patients in Group LM received 19 ml of 0.5% levobupivacaine with preservative free midazolam in a dose of 50μg/kg in 1mL normal saline for supraclavicular brachial plexus block using ultrasound guidance. To ensure blinding, the study solution was prepared by an anesthesiologist who was not aware of the study protocol. The anesthesiologist who assessed the parameters was also blinded to group allocation.

Study Protocol and Procedure

Pre-anaesthetic evaluation of the patients was performed before the surgery. Patients were given tablet alprazolam (0.5 mg) and tablet ranitidine (150 mg) orally, the night before surgery and a fasting of 6 hours was ensured. On the day

of surgery, in the operating room, a venous access was established in the contralateral limb and Ringer's lactate was started at the rate of 10ml/kg. Monitoring of heart rate (HR), systemic blood pressure (NIBP), electrocardiogram (ECG), and peripheral oxygen saturation (SpO_2) was commenced. Patients were not premedicated for the procedure. All the blocks were performed by the same senior anesthesiologist using transportable ultrasound system (Sonosite Micromax, Sonosite Inc., Bothell, Wa, USA) with a 38 mm 8-13 MHz linear high-frequency ultrasound transducer (HFL-38) After visualization of brachial plexus by ultrasound probe, the study drug was administered with an echogenic 21 gauge Sonoplex Stim Cannula, Pajunk ® around the brachial plexus according to randomization schedule for Group LS or Group LM.

Sensory block was confirmed by a loss of cold sensation using an alcohol swab and pinprick sensation using a 25 G hypodermic needle in all dermatomes of the brachial plexus (C5 – T1). This decrease in sensation was judged by a rupee scale, in which the patients were asked to evaluate the decrease in sensation in terms of a fraction of a rupee (say for *e.g*. if the patient said there is a decrease in sensation by 50 paise it was interpreted as a decrease in sensation by 50%). The onset of sensory block was defined as a decrease of sensation to 25% or less by pinprick in comparison to contralateral limb as a reference. It was evaluated at 1, 2, 4, 6, 8, 10, 12 and 15 min. and thereafter every five minutes until the efficacy or failure of the blockade was identified. Sensory block duration was defined as the time elapsed between injection of the drug and demand for rescue analgesia.

Motor block was determined according to a modified Lovett rating scale ranging from 6 (usual muscular force) to 0 (complete paralysis) along with thumb abduction for the radial nerve, thumb adduction for the ulnar nerve, thumb opposition for the median nerve and flexion of the elbow for the musculocutaneous nerve [7].

Motor block onset was defined as a reduction of muscle force to 3 or less. It was evaluated at 1, 2, 4, 6, 8, 10, 12 and 15 min and thereafter at every five minutes until the efficacy or failure of the blockade was identified. Motor block duration was defined as the time interval between the onset of the block and the recovery of complete motor function of the hand and forearm of the blocked limb. At the end of 30 min, if there were no signs of motor and sensory block, it was considered failed block, such patients were conducted under general anaesthesia and patients were excluded from the study.

Blood pressure, heart rate, peripheral oxygen saturation and sedation scores were monitored intraoperatively for every 10 mins after the block was given and thereafter every 30 mins for the first 2 hours postoperatively. Level of sedation was assessed using sedation scale [8].

The pain was assessed using a VAS Scale where zero (0) represents no pain, and 10 means the worst possible pain. The rescue analgesia (inj. Tramadol 2 mg/kg intravenously) was given when the patient complained of pain (VAS Score > 3). The sensory block, the motor block, and the pain scores were monitored every 2 hourly till 4 hrs and then 4 hourly till 12 hrs postoperatively. In the event that the block had been deemed by the patient to have worn off between the last assessment and present assessment, the time in which the patient noted block waning during this period was noted.

After completion of the study, the collected data was tabulated as mean± SD and compared by with the help of Windows Excel 2007, Stat graphics Centurion 16 (Stat point Technologies Inc, Warrenton, Virginia). The demographic data for categorical variables was compared using chi-square test and statistical significance in mean difference was done by using analysis of variance (ANOVA). A p-value < 0.05 was considered statistically significant.

RESULT

The present study has evaluated the clinical efficacy of midazolam as an adjuvant to levobupivacaine for supraclavicular brachial plexus block. No patients were excluded from the study and data of all patients' data was analyzed for statistical significance. All patients were cooperative for assessment of block characteristics.

The demographic profile of the patients was comparable in both the group in terms of age weight, gender distribution, ASA physical status and duration of surgery (Table **1**).

Time to sensory onset was significantly lower in patients of Group LM than Group LS(12.19 ± 0.45 min *vs*. 19.33 ± 2.24 mins). The mean duration of sensory blockade (analgesia) was found to be significantly prolonged in patients of Group LM compared to Group LS(537.6 ± 101.01 mins *vs*. 319.80 ± 87.09 mins) (Table **2**).

Time to motor onset was also found to be significantly lower in patients of group LM compared to group LS (9.58 ± 2.39 min *vs*. 14.62 ± 3.62 mins) (Table **2**). The mean duration of motor blockade was found to be significantly enhanced in Group LM (405.0 ± 61.62 mins) compared to Group LS (274.8 ± 46.30 mins) (Table **2**).

Table 1. Demographic profile.

Parameters	Group LS	Group LM	P value
Age (yr)	32.5±2.47	33.1±1.46	0.3010
Weight (kg)	59.2±7.87	60.4±8.87	0.6159
M:F	15/10	13/12	0.5688
ASA I/II	20/5	18/7	0.5078
Duration of surgery (mins)	90.75 ± 32.60	94.25 ± 30.50	0.55

Data are presented as mean ±SD or absolute number; P value > 0.05 is statistically non-significant.

Table 2. Block characteristics.

Parameter (in mins)	Group LS	Group LM	P value
Onset of sensory block	19.33 ± 2.24	12.19 ± 1.45	<0.0001
Duration of sensory block (analgesia)	319.8 ± 65.4	537.6± 131.4	<0.0001
Onset of motor block	14.62 ± 3.6	9.58 ± 2.38	<0.0001
Duration of motor block	274.8 ± 66.6	405 ±118.8	<0.0001

Data are presented as mean ±SD or absolute number; P value > 0.05 is statistically non-significant.

VAS scores were higher in patients of Group LS (Table **3**). All the patients in Group LS received rescue analgesia by 6 hours whereas, in Group LM, it was by 9 hr. There was no significant difference in the baseline or intraoperative sedation scores between the groups. Average sedation score in both the group was one.

Table 3. Pain scores (VAS Scores).

Time (in hours)	Group LS	Group LM	P value
2^{nd}	0	0	-
4^{th}	4.2 ±1.5	0	<0.001
8^{th}	6.32 ±1.5	2.13±1.1	<0.001
12^{th}	8.1±1.2	3.0±0.5	<0.001

Data are presented as mean ±SD or absolute number; P value > 0.05 is statistically non- significant.

Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation were comparable between groups and did not vary significantly in the intraoperative and postoperative period. No incidence of hypotension, respiratory depression (respiratory rate < 10 breaths/ min. or SpO_2 < 90% on air), drowsiness (sedation) or any other study drug related adverse effects occurred in the in any patient of either group.

DISCUSSION

In this study, we found that when midazolam is added to levobupivacaine for supraclavicular brachial plexus block it shortens sensory and motor block onset time and extends block durations.

Considering the greater systemic toxicity potential and the cardiovascular effects of the racemic bupivacaine, levobupivacaine seems a good replacement for brachial plexus block. Cox CR *et al*. compared levobupivacaine with bupivacaine for supraclavicular brachial plexus block and concluded that due to reduced toxic potential of levobupivacaine, there is the increased margin of safety of levobupivacaine in regional anaesthesia [9]. Ultrasound guidance facilitates in dose reduction of local anaesthetics in peripheral nerve blocks. Raju PKBC in his review article clearly described the advantage of ultrasound guidance in dose reduction of local anaesthetics during peripheral nerve blocks [10]. Tiwari P *et al*. used the 20ml total volume of (19ml ropivacaine+1ml study drug) for a supraclavicular block in their study [11]. The most common total volume used for ultrasound-guided supraclavicular brachial plexus block is 20 to 25 mL [12]. So 20ml (19mllevobupivacaine+1ml midazolam) was used in present study.

Limited research has been done on the effect of midazolam as an adjuvant to local anaesthetics in peripheral nerve blocks. Till date, there is no study on the effect of adding midazolam to levobupivacaine, on block characteristics and

duration of analgesia, in supraclavicular brachial plexus block. Koj Jorbo, *et al*. studied midazolam for the first time in brachial plexus block in a dose of 50 μg/kg, with the reason that others have used the same dose of midazolam in the central neuraxial block without any significant adverse effects [13]. Other studies have also used midazolam in the same dose. Hence in our study, midazolam in a dose of 50 μg/kg was used.

Various studies have demonstrated the presence of GABA receptors in peripheral nerves and the action of midazolam on GABA receptors is well established. Extrasynaptic receptors for GABA are present on myelinated axons of peripheral nerves. Brown and Marsh demonstrated GABA receptors in a mammalian peripheral nerve trunk [14]. Morris ME *et al*. stated that extrasynaptic receptors for GABA are present on the myelinated axons of peripheral nerves [15]. Cairns *et al*. observed the presence of GABA receptors within the temporomandibular joint and its activation could decrease the transmission of nociceptive signals [16].

In our study, we observed that the onset of sensory and motor blocks was significantly enhanced in patients who received a combination of midazolam and levobupivacaine. This could be due to a local anaesthetic property of midazolam and its synergistic action with local anaesthetics [17].

In the present study, the mean duration of sensory block in midazolam group was 537.6mins while 319.8mins in levobupivacaine group (P = 0.0001). The mean duration of motor block in midazolam group was 405min while 274.8min in levobupivacaine group (P = 0.0001). In addition, patients in the midazolam group showed clinically and statistically significantly lower pain scores (Table **3**). The prolonged analgesia in Group LM could be due to the action of midazolam on GABA-A receptors present in the brachial plexus which produce antinociceptive effects [5, 6].

N Laiq *et al*. in their study used 50μg/kg midazolam with 30ml 0.5% bupivacaine in supraclavicular brachial plexus block and concluded that addition of midazolam to bupivacaine hastened the onset and prolonged the duration of sensory and motor blockade of the brachial plexus. It also improved the postoperative analgesia without producing any adverse effects compared to plain bupivacaine (0.5%) in equal volume [18]. Results of the present study are similar to their study.

Similarly, SI Shaikh *et al*. in their study also used 0.05mg/kg midazolam with 30ml 0.5% bupivacaine and compared with bupivacaine alone for supraclavicular brachial plexus block and concluded that addition of midazolam to bupivacaine for supraclavicular brachial plexus block prolonged motor blockade (Group B 450.48±57.95min and Group BM 608.96±157.75mins) and post-operative analgesia (Group B 502.24±52.68min and Group BM 805.04±175.75min) without increasing the risk of adverse effects [19]. Though results are similar to present study but relatively more duration of motor block and analgesia observed, could be due to more volume of local anaesthetic used by SI Shaikh *et al*.

In a study by Koj Jorbo *et al*. midazolam added to bupivacaine in supraclavicular brachial plexus block has enhanced the onset of sensory block and motor block with statistically significant difference ($p<0.05$). There were no statistically significant hemodynamic changes in either group and pain scores were also significantly lower in midazolam group [13]. In our study also hemodynamic changes in both the groups were similar and pain scores were also significantly lower in midazolam group.

In our study sedation scores were similar in both the groups, whereas, in other studies, sedation scores were relatively higher in midazolam group. The amnestic effects of midazolam are more potent than its sedative effects. Thus, patients may be awake following administration of midazolam but remain amnestic for events and conversations (postoperative instructions) for several hours [20]. The probable explanation is the fact that short duration of action of a single dose of midazolam is due to its lipid solubility, leading to rapid redistribution from the brain to inactive tissue sites as well as rapid hepatic clearance (6-8mL/kg/min) so the smaller doses that were used in present study could have cleared faster and hence unable to produce sedation [20].

CONCLUSION

Midazolam as an adjuvant to 0.5% levobupivacaine has enhanced the duration of sensory and motor block of supraclavicular brachial plexus block. It did not lead to sedation and there were no drug or technique related adverse effects.

LIMITATION OF STUDY

No sedatives were used while the block was performed as literature suggested midazolam as adjuvant produces

sedation.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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