International Journal Dental and Medical Sciences Research
Volume 2, Issue 5, pp: 68-72 www.ijdmsrjournal.com ISSN: 2582-6018

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

Salma Mariyam[1], *Sadia Ali Wani[2], Rohit Reddy Vuppula[3], Nalin Vilochan[4], Surinder Singh Sodhi[5], Pankaj Kumar[6], Praveena Venkat Reddy Redum [7]

[1]*Senior Resident, Department of Anesthesiology and Critical Care, GMC Rajouri.*
[2] *Senior Resident, Department of Anesthesiology and Critical Care, GMC Srinagar*
[3] *PG Resident, Department of Anesthesiology and Critical Care, MMIMSR Haryana*
[4]*PG Resident, Department of Anesthesiology and Critical Care, MMIMSR Haryana*
[5]*Senior Resident, Department of Anesthesiology and Critical Care, MMIMSR Haryana*
[6] *PG Resident, Department of Anesthesiology and Critical Care, MMIMSR Haryana*
[7] *PG Resident, Department of Anesthesiology and Critical Care, MMIMSR Haryana*
Corresponding Author:Dr Sadia Ali Wani

Date of Submission: 01-10-2020 Date of Acceptance: 25-10-2020

ABSTRACT:Background: The present study was conducted 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 aim was to determine the duration of sensory and motor block and secondary aims were sedation score and any other complications.

Materials and Methods:100 patients were randomly selected and dividedinto two groups of 50 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 nerve 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 (542.6± 134.4 vs. 324.8 ± 68.4mins). The mean duration of motor blockade was also significantly enhanced in patients of Group LM (410 ±111.8 mins) compared to Group LS (280.8 ± 69.6 mins). VAS scores were higher in Group Levobupivacaine than group midazolam. 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.

I. INTRODUCTION

Levobupivacaine is a relatively new long-acting local anesthetic (LA). The pharmacological activity of levobupivacaine is similar tothat of bupivacaine [1]. The levobupivacaine emerged after few extreme cases of cardiotoxicity by D-isomer of bupivacaine [2, 3]. Levobupivacaine has similar activity and better tolerability with less cardiotoxicity and neurotoxicity which makes it a better alternative [4].

In search of improving the quality of nerve block and duration of the nerve block, over the years, many adjuvants have been used with LA. We are constantly trying to search for new alternatives and it is going on since every drug has its benefits and side effects.

Midazolam, a benzodiazepine is a water-solubleand low cost drug. It is known to produce antinociception thereby enhances the effect of LA when used as an adjuvant to central neuraxial block. The mechanism of action of midazolam is due to its action on GABA-A receptors. In case of peripheral regional blocks with LA, the receptors (Extra-synaptic)for GABA are present on myelinated axons of peripheral nerves[5, 6].

The present prospective study was used to assess the clinical efficacy of midazolam as an adjuvant to

International Journal Dental and Medical Sciences Research
Volume 2, Issue 5, pp: 51-54 www.ijdmsrjournal.com ISSN: 2582-6018

0.5% levobupivacaine for ultrasound-guided supraclavicular brachial plexus block.

II. AIMS AND OBJECTIVES:

1. To compare duration of sensory block between the twogroups
2. To compare duration of motor block between the two groups
3. To compare level of sedation and any other complication in the two groups

III. MATERIAL AND METHODS

100 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 randomized prospective study. Exclusion criteria included the following: bleeding disorder, h/o injury to brachial plexus, drug allergy, chronic opiod user, epileptic disorder, liver or kidney insufficiency, disease of cardiorespiratory system, peripheral nerve problems, psychiatric problems and infection at injection site.

100 patients were recruited and randomly allocated into two equal groups of 50 patients each. The subjects in Group LS received 19 ml of 0.5% concentration of levobupivacaine with 1 ml normal saline and subjects in Group LM received 19 ml of 0.5% concentration of levobupivacaine with preservative free midazolam in a dose of 50µg/kg in 1mL normal saline for supraclavicular brachial plexus block using ultrasound guidance. Ethical clearance was taken from the institutional ethical committee and informed consent was taken from all the participants

Study Protocol and Procedure

Pre-anesthetic evaluation of all the patients in this was performed before the surgery. Patients were prescribed tablet alprazolam (0.5 mg) and tablet ranitidine (150 mg) orally, the night before surgery and a fasting(NPO) of 6 hours was ensured. Just before starting the surgery, a venous access was established in the OT(operating room) in the opposite limb and Ringer's lactate solution was started(10ml/kg).

Monitoring of heart rate (HR), systemic blood pressure (NIBP), electrocardiogram (ECG), and peripheral oxygen saturation (SpO_2) was started. Patients were not premedicated for the procedure. The nerve blocks were performed by the same clinicianafter proper visualization with ultrasound probe.

loss of cold sensation confirmed sensory block which was done by using an alcohol swab and pinprick sensation. In order to quantify, a rupee scale was used to judge the decrease of sensation (e.g. when the subject said there is a decrease in sensation by 50 paise it meant there is a decrease in sensation by 50%). The onset of sensory block was considered when the sensation decreased to 25% or less by pinprick in comparison to opposite limb as a reference point. This sensation was evaluated at time intervals at 1, 2, 4, 6, 8, 10, 12 and 15 min. and afterwords every five minutes until the block failure was identified. The sensory nerve block duration was defined as the time taken between the injection of the LA and the demand for rescue analgesia.

A modified Lovett rating scale was used to assess motor block which ranged from 6 (which means usual muscular force) to 0 (means complete paralysis) along with abduction of thumb for the radial nerve, adduction of thumb for the ulnar nerve, thumb opposition for the median nerve and elbow flexion for the musculocutaneous nerve [7].

The onset of motor block was defined as a muscle reduction force to 3 or less and was evaluated at 1, 2, 4, 6, 8, 10, 12 and 15 min and afterwards at every five minutes until the block failure was identified. The duration of Motor block 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 anesthetized limb. At the end of half an hour, if there were no signs of motor and sensory block, it was considered failure of the nerve block, and such subjects were done under general anesthesia and those subjects were excluded from this study

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

VAS Scale was used for assessing pain where zero (0) represents no pain, and 10 means the worst possible pain. The rescue analgesia (Tramadol injection intravenously in the dosage of 2 mg/kg) was given when subjects VAS score for pain reached >3. The sensory nerve block, the motor nerve block, and the pain scores(VAS) were noted at 2 h, 4h, 8h, 12h, postoperatively. In the case in which 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 collection of data, it was tabulated as mean± SD. Chi square test and ANOVA was used for

International Journal Dental and Medical Sciences Research
Volume 2, Issue 5, pp: 68-72 www.ijdmsrjournal.com ISSN: 2582-6018

comparison. A p-value < 0.05 was considered statistically significant.

IV. RESULT

The demographic characteristics of the patients was not statistically significant between the two groups in terms of age, weight, gender distribution, ASA physical status and duration of surgery (Table **1**). That means the two groups were comparable.

The onset time of sensory block was significantly lower in patients of Group LM than Group LS(13.19 ± 1.47 min vs. 20.33 ± 2.24 mins).

The mean duration of sensory blockade (analgesia) was significantly prolonged in Group LM compared to Group LS(542.6 ± 134.4 mins vs. 324.80 ± 68.4 mins) (Table **2**).

The onset time of motor block was also found to be significantly lower in patients of group LM compared to group LS (10.2 ± 2.39 min vs. 15.62 ± 3.7 min) (Table **2**).

The mean duration of motor block was significantly increased in Group midazolam(LM) (410 ±111.8mins) when compared to Group levobupivacaine (LS) (280.8 ± 69.6mins) (Table **2**).

Table 1. Demographic characteristics.

Parameters	Group LS	Group LM	P value
Age (yr)	32.5±2.47	33.1±1.46	0.29
Weight (kg)	59.2±7.87	60.4±8.87	0.62
M:F	30/20	26/24	0.57
ASA I/II	40/10	35/15	0.51
Duration of surgery (mins)	90.75 ± 32.60	94.25 ± 30.50	0.57

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	20.33 ± 2.24	13.19 ± 1.47	<0.0001
Duration of sensory block (analgesia)	324.8 ± 68.4	542.6± 134.4	<0.0001
Onset of motor block	15.62 ± 3.7	10.2 ± 2.39	<0.0001
Duration of motor block	280.8 ± 69.6	410 ±111.8	<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 wasone.

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.

V. DISCUSSION

Racemic bupivacaine has greater systemic toxicity and serious cardiovascular effects, solevobupivacaine seems to be a good replacement for brachial plexus block. A study was conducted by Cox CR et al. to compare thelevobupivacaine with bupivacaine for

supraclavicular brachial plexus block and concluded that levobupivacaine has greater margin of safety than bupivacaine [9]. Ultrasound guidance facilitates by locating the exact location of nerve and thereby helps in reducing the dosage required in peripheral nerve blocks. Raju PKBC published a review article clearly describing the advantage of US guidance in dose reduction of LA during peripheral nerve blocks [10]. Tiwari P et al. used the total of 20ml volume of (19ml ropivacaine+1ml study drug) for a supraclavicular nerve block in their study [11]. 20 to 25 mL of LA is mostly used for supraclavicular blocks [12]. In this study, we used 20ml (19mllevobupivacaine+1ml midazolam) of LA.

Limited data is available on the effect of midazolam as an adjuvant to LA in peripheral nerve blocks. To the best of our knowledge, there is no study on the effect of adding midazolam to levobupivacaine, on block characteristics andduration of analgesia, in supraclavicular brachial plexus block, done in india. KojJorbo, et al. suggested 50 µg/kg of midazolam for supraclavicular blocks, and the reason given by Jorbo et al was that the similar dosage(50 ug/kg) of midazolam is used in the central neuraxial blocks without any significant side effects [13]. There are many studies which have used the similar dosage for midazolam. That is the reason in this study, midazolam in a dose of 50 µg/kg was used.

Different studies proposed that the GABA receptors are present in peripheral nerves and the mechanism of action of midazolam on GABA receptors is well known. The GABA receptors (extra-synaptic) are present on myelinated axons of peripheral nerves. Brown and Marsh in one of their studies demonstrated that the GABA receptors are present in a mammalian peripheral nerve trunk [14]. Morris ME et al. stated that extra-synaptic receptors for GABA are present on the myelinated axons of peripheral nerves [15]. The presence of GABA receptors have been found in the temporomandibular jointsby Cairns et al. and activation of these receptors could decrease the transmission of pain signals[16].

In present 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 anesthetic property of midazolam and its synergistic action with local anesthetics [17].

In the current study, the mean duration of sensory block in midazolam group was prolonged when compared with levobupivacaine group, which was statistically significant. The mean duration of motor block in midazolam group was 410min while 280.8min in levobupivacaine group, which was statistically significant. In addition to this, the subjects in the LM group showed clinically and statistically significantly lower pain scores (Table **3**). The prolonged sensory block in midazolam group could be due to the action on peripheral GABA-A receptors present in the supraclavicular brachial plexus which produce analgesic effects [5, 6]. This was in agreement with N Laiqet al., who used 50µg/kg midazolam with bupivacaine.

Similarly, SI Shaikh et al. used 50 ug/kg midazolam with 30ml 0.5% bupivacaine and concluded that addition of midazolam prolonged motor blockade and post-operative analgesia without increasing adverse side 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 anesthetic used by SI Shaikh et al.

In a study by KojJorboet al., the addition of midazolam to bupivacaine hasenhanced both the onset of sensory block and motor block ($p<0.0001$).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 midazolamgroup.

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].

VI. CONCLUSION

Midazolam can be used as an adjuvant to 0.5% levobupivacaine. 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.

REFERENCES

[1]. Arias MG. Levobupivacaine-A long-acting local anaesthetic, with less cardiac and neurotoxicity. Update Anaesth 2002; 14(7):23-5.
[2]. Davis NL, de Jong RH. Successful resuscitation following massive bupivacaine overdose. AnesthAnalg 1982; 61(1): 62-4.
[3]. McCloskey JJ, Haun SE, Deshpande JK. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. AnesthAnalg 1992; 75(2): 287-90.
[4]. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs 2000; 59(3): 551-79.
[5]. Morris ME, Di Costanzo GA, Fox S, Werman R. Depolarising action of GABA on myelinated fibers of peripheral nerves. Brain Res 1983; 278: 117-26.
[6]. Liske S, Morris ME. Extrasynaptic effects of GABA agonists on myelinated axons of peripheral nerves. Can J PhysiolPharmacol 1994; 72: 368-74.
[7]. Duma A, Urbanek B, Sitzwohl C, Kreiger A, Zimpfer M, Kapral S. Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: a randomized, controlled study. Br J Anaesth 2005; 94(1):112-6.
[8]. Koroglu A, Demirbilek S, Teksan H, Sagir O, But AK, Ersoy MO. Sedative, haemodynamic and respiratory effects of dexmedetomidine in children undergoing magnetic resonance imaging examination: preliminary results. Br J Anaesth 2005; 94(6): 821-4.
[9]. Cox CR, Faccenda KA, Gilhooly C, Bannister J, Scott NB, Morrison LM. Extradural S(-)-bupivacaine: comparison with racemic RS- bupivacaine. Br J Anaesth 1998; 80(3):289-93.
[10]. Raju PK. Ultrasound-guided brachial plexus blocks. Br J Anaesth: Contin Educ Anaesth Crit Care Pain 2014; 14:185-91.
[11]. Tiwari P, Jain M, Rastogi B, Aggarwal S, Gupta K, Singh VP. A comparative clinical study of perineural administration of 0.75% ropivacaine with and without dexmedetomidine in upper limb surgery by ultrasound guided single injection supraclavicular brachial plexus block. Global AnesthPerioper Med 2015; 1: 131-3.
[12]. AdmirHadzic A. Carrera, T Clark, J Gadsden, M Karmaker, X Sala-blanch Ultrasound-guided supraclavicular block Hadzic's Peripheral nerve blocks and anatomy for ultrasound guided nerve blocks. 2nd ed. Mac Graw Hill2012.
[13]. Jarbo K, Batra YK, Panda NB. Brachial plexus block with midazolam and bupivacaine improves analgesia. Can J Anaesth 2005; 52(8): 822-6. [http://dx.doi.org/10.1007/BF03021776]
[14]. Brown DA, Marsh S. Axonal GABA-receptors in mammalian peripheral nerve trunks. Brain Res 1978; 156(1): 187-91.
[15]. Morris ME, Di Costanzo GA, Fox S, Werman R. Depolarizing action of GABA (γ-aminobutyric acid) on myelinated fibers of peripheral nerves. Brain Res 1983; 278(1-2): 117-26.
[16]. Cairns BE, Sessle BJ, Hu JW. Activation of peripheral GABAA receptors inhibits temporomandibular joint-evoked jaw muscle activity. J Neurophysiol 1999; 81(4):1966-9.
[17]. Raghu R, Indira P, Kiran M, Radharamana M. A comparative study of 0.375% bupivacaine with midazolam and 0.375% bupivacaine for brachial plexus block in upper limb surgeries. Asian Pac J Health Sci 2015; 2:129-35.
[18]. Laiq N, Khan MN, Arif M, Khan S. Midazolam with bupivacaine for improving analgesia quality in brachial plexus block for upper limb surgeries. J Coll Physicians Surg Pak 2008; 18(11):674-8.
[19]. ShaikhSI,Veena K.Midazolamasanadjuvant in supraclavicular brachial plex us block.Anaesth Pain Intensive Care 2012;16:7-12.
[20]. Stoelting RK, Hiller SC. Benzodiazepines. Pharmacology and Physiology in Anaesthetic Practice. 4thed. Lippincott William Wilkins 2006.