

Prospective Randomised Study to Evaluate the Efficacy of Midazolam as an Adjuvant to Local Anaesthetics in Brachial Plexus Block

Sarita Fernandes¹, Vivek Deshmukh²

ABSTRACT

Introduction: Adjuvants are used to potentiate the action of local anaesthetics and prolong the duration of analgesia. Midazolam, a water soluble benzodiazepine is known to possess antinociceptive effects. It has been used epidurally and intrathecally in combination with local anaesthetics. Our study aimed to evaluate the efficacy and safety of midazolam added to brachial plexus anaesthesia.

Material and Methods: This was a prospective, randomised, double blind study in 60 ASA I or II patients undergoing upper limb surgeries under supraclavicular brachial plexus anaesthesia. Group BLM(n=30) received Inj Bupivacaine (0.5%) 20ml + Inj Lignocaine (2%) 10ml with adrenaline (1:200000) + Inj Midazolam 50 mcg/kg. Group BL (n=30) received Inj Bupivacaine (0.5%) 20ml + Inj Lignocaine (2%) 10ml with adrenaline (1:200000). We compared onset and duration of sensory and motor block, hemodynamic variables, pain and sedation scores and post-operative analgesic requirements.

Results: There was statistically significant difference ($P < 0.001$) in the onset of sensory block in group BLM (2.37±1.54min) as compared to group BL(6.33±3.20min). Onset of motor block was faster in group BLM (2.57±1.68 min) than group BL (7.33 ± 3.41 min.) ($P < 0.001$). Duration of sensory block was significantly longer ($P = 0.004$) in group BLM (19.20± 5.98 hr) versus group BL (14.6±6.04 hr.) Motor block was prolonged in group BLM (9.4±3.02 hr) compared to group BL (6.87±2.45 hr). ($P = 0.001$). Mean postoperative Pain scores were lower in group BLM than in group BL ($P < 0.05$). In the post-operative period 6.67% patients in group BLM demanded analgesia as compared to 63.33% in group BL. ($P < 0.001$)

Conclusion: Midazolam (50 ug/kg) as an adjuvant hastens the onset and prolongs the duration of both sensory and motor block and reduces post-operative analgesic requirements.

Keywords: supraclavicular brachial plexus block, bupivacaine, lignocaine, adjuvants, midazolam

and dense anaesthesia targets the brachial plexus trunks. At this location the sensory, motor and sympathetic innervation which is carried in three nerve structures is limited to a minute region.^{2,3} However the limited period of analgesia may prove to be a drawback in case the duration of surgery is prolonged. Bupivacaine has been the local anaesthetic most frequently used due to its longer duration of action but has a ceiling dose and potential for cardiotoxicity. This can be overcome by continuous regional anesthesia techniques using catheters or malleable needles but these have their own problems. Adjuvants added to local anaesthetics have been found to enhance the quality of the block and decrease the requirement of local anaesthetics. Various studies have investigated several adjuvants, including opioids, clonidine, neostigmine, hyaluronidase, and bicarbonate⁴⁻⁸ Midazolam, a water-soluble benzodiazepine, is known to produce antinociception and to enhance the effect of local anaesthetic when given epidurally or intrathecally.⁹⁻¹¹ Midazolam produces this effect by its action on gamma amino butyric acid-A (GABA-A) receptors which have also been found in peripheral nerves.¹²⁻¹⁴ At our institute we routinely use a combination of bupivacaine and lignocaine for the brachial plexus block. We carried out this study to evaluate if the addition of midazolam improved the quality of the block and any adverse effects that could arise by its inclusion.

MATERIAL AND METHODS

This was a prospective, randomised, double blind study conducted after institutional ethics committee approval and written informed consent from the patients. 60 patients scheduled for elective or emergency surgeries on the forearm or hand were enrolled for the study. We included ASA I and II patients of either gender, aged 18-60 year, weighing 40-70kg. Patients with bleeding disorders or receiving anticoagulants or chronic analgesic therapy and those with contralateral hemidiaphragmatic paralysis, vocal cord palsy, h/o allergy to the study drugs were excluded. Patients were divided into 2

INTRODUCTION

Brachial Plexus Block is a feasible alternative to general anaesthesia for upper limb surgeries. The profound muscular relaxation provides good operating conditions and the intense analgesia which extends into the post-operative period decreases the demand for pain relief. Intraoperative hemodynamics are better maintained and the associated sympathetic block decreases vasospasm, edema and post-operative pain.¹ There are various approaches to block the brachial plexus namely the interscalene, supraclavicular, infraclavicular and axillary approach. Of these the supraclavicular technique is commonly used for surgeries on the forearm and hand. This block which provides faster

¹Additional Professor, ²Ex-Senior Resident, Department of Anaesthesia, Topiwala National Medical College and BYLNair Charitable Hospital, Mumbai Central, Mumbai 400008, Maharashtra, India

Corresponding author: Dr Sarita Fernandes, A-6-20, Flat No 23, Indra Dhanush, Jeevan Bima Nagar, Borivili(West), Mumbai 400103, Maharashtra, India

How to cite this article: Sarita Fernandes, Vivek Deshmukh. Prospective randomised study to evaluate the efficacy of midazolam as an adjuvant to local anaesthetics in brachial plexus block. International Journal of Contemporary Medical Research 2016;3 (5):1542-1546.

groups using computer generated randomisation.

Group BLM (study group)

Inj Bupivacaine (0.5%) 20ml + Inj Lignocaine (2%) 10ml with adrenaline (1:200000) + 50 mcg/kg of Midazolam

Group BL (control group)

Inj Bupivacaine (0.5%) 20ml + Inj Lignocaine (2%) 10ml with adrenaline (1:200000)

Care was taken to note that the safe upper dose limit of the drugs was not exceeded. The solution to be injected was made by an anaesthetist not involved in performing the block, patient care or data collection. The block was performed by a senior and experienced anaesthesiologist. All patients were premedicated with 1-2 mcg/kg Fentanyl i.v. With the patient in the supine position and the head turned to the opposite side and the ipsilateral arm adducted. The interscalene groove was identified and the finger was moved towards the clavicle to palpate the subclavian artery. The stimulating insulated needle [STIMUPLEX 22 G 50 mm] was inserted just above the palpating finger and advanced in a direction caudad running parallel to the sagittal axis until any two of the following motor responses were elicited.

I] Upper arm: - flexor - biceps, extensor - triceps

II] Fore arm: - extensor - brachioradialis, wrist extensors,

III] Hand: - flexors or extensors of the fingers.

We initially used a current of 0.8 mA frequency 1 Hz to elicit the desired motor

response. The current was gradually reduced to obtain the best possible motor response at a current of 0.6 mA. The current was further reduced to 0.2 mA to rule out the intraneural placement. The needle was repositioned and the drug solution injected on

obtaining the best response at 0.4- 0.6 mA after confirming negative aspiration for blood.

The following parameters were studied.

1] **Onset of sensory block**:- the time from injection till there was absence of sensation in the areas supplied by medial, radial, ulnar and musculocutaneous nerves measured at 0, 2, 5, 10, 20 and 30min

0= no block (normal sensation)

1= partial block (decreased sensation)

2= complete block (no sensation)

A cotton swab dipped in spirit was used to test the sensory block.

2] **Onset of motor block**: - Motor block was measured at 0,2,5,10,20, and 30 min by assessing the following motor functions i.e. flexion at elbow (musculocutaneous nerve), wrist and elbow extension, opposition of thumb and index finger (median nerve) and opposition of thumb and little finger (ulnar nerve).

Motor block was graded as:

0= no block (full muscle activity)

1= partial block (decreased muscle activity)

2= complete block (no muscle activity)

3] **Duration of sensory block**:-Time elapsed between injection of the drug and appearance of pain requiring analgesia.

4] **Duration of motor block**: Time elapsed between injection of the drug to complete return of motor power.

5] **Hemodynamic parameters**: Heart rate, systolic and diastolic blood pressure and arterial oxygen saturation (SpO₂) were measured at 0, 2, 5, 10, 20, 30 min and thereafter every 15 min till the end of surgery.

6] Sedation was assessed using the Ramsay sedation score at 0, 2, 5, 10, 20, 30 min and repeated every 15 min till surgery was completed.

1 Anxious or restless or both

2 Cooperative, orientated and tranquil

3 Responding to commands

4 Brisk response to stimulus

5 Sluggish response to stimulus

6 No response to stimulus

7] Pain score using visual analogue scale where 0 is no pain and 10 is worst possible pain s(VAS): was recorded at 6,12 and 24 hr post-operative period

8] Number of patients demanding analgesia in the post-operative period: Analgesia in the form of injection diclofenac was given on demand by the patient or when the VAS score was ≥ 3

Only patients with complete sensory and motor block were included in the study. Patients who had to be supplemented general anaesthesia at any time during the intraoperative period were excluded from the study.

According to previous studies¹⁵ all the patients (100%) in the plain bupivacaine group needed rescue analgesia whereas only 15% demanded analgesia in the bupivacaine plus midazolam group. A power analysis indicated that a sample size of 60 was sufficient to detect a large statistical difference with an $\alpha = 0.05$

STATISTICAL ANALYSIS

Statistical Analysis was performed using SPSS version 15. All results were expressed as Mean \pm SD. Comparison of the demographic variables, hemodynamic parameters, onset and duration of sensory and motor block was performed using the unpaired t test. Sedation and pain scores at various intervals were compared with Mann Whitney U test while the post-operative analgesic requirements were compared using Chi square test.

RESULTS

Demographic variables(age, gender distribution and weight) were comparable. Duration of surgery was similar. Onset of sensory block occurred earlier in group BLM (2.37 \pm 1.54 min) as compared to group BL (6.33 \pm 3.20) ($P < 0.001$). Onset of motor block in Group BLM was also faster (2.57 \pm 1.68min) versus Group BL 7.33 \pm 3.41min ($P < 0.001$). Duration of sensory block in Group BLM was longer (19.20 \pm 5.98hr) as compared to Group BL(14.60 \pm 6.04 hr) ($P = .004$). The motor block also lasted longer in Group BLM (9.40 \pm 3.02 hr) versus Group BL (6.87 \pm 2.45 hr) ($P < .001$)

Sedation scores were comparable during the intra and post-operative period. The post-operative pain scores at 6,12 and 24hr were lower in group BLM as compared to group BL (P

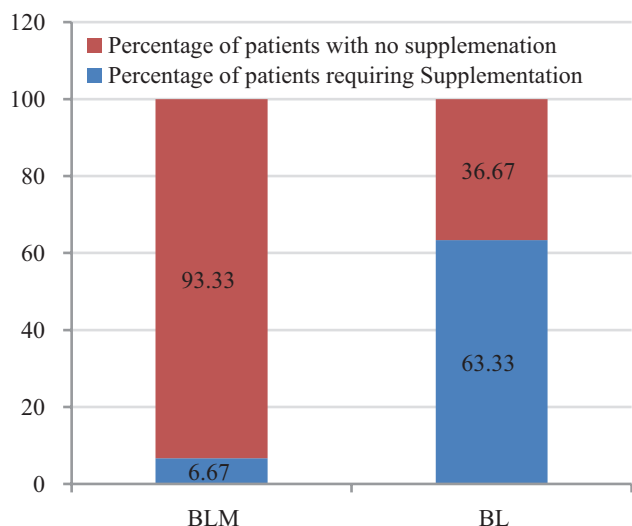
Parameter	Group BLM			Group BL			Unpaired t test	P value
	Mean	SD	Range	Mean	SD	Range		
Onset of sensory block(min)	2.37	1.54	2-10	6.33	3.20	5-20	6.119	P< .001
Onset of Motor block(min)	2.57	1.68	2-10	7.33	3.41	5-20	6.877	P< .001
Duration of sensory block (hours)	19.20	5.98	12-24	14.60	6.04	6-24	2.965	P = 0.004
Duration of motor block (hours)	9.40	3.02	6-12	6.7	2.45	2-12	3.568	P< .001

Table-1: Time for Onset and Duration of Sensory and Motor block

Group		Number of Patients Required Supplements		Total
		Yes	No	
Group BLM	Count	2	28	30
	Percent	6.67%	93.3%	100%
Group BL	Count	19	11	30
	Percent	63.33%	36.67%	100%
Total	Count	21	39	60
	Percent	35.0%	65.0%	100%

Table-2: Number of Patients requiring analgesics in the 24 hour post-operative period

Chi-Square Test	Value	Df	P value	Association
Pearson Chi-Square	21.17	1	<0.0001	Significant
Fisher's Exact Test			<0.0001	Significant



Graph-1: Comparison between the number of patients who required analgesic supplementation in the 24 hour post-operative period

< 0.05).

The number of patients who demanded post-operative analgesia were significantly less in group BLM(6.67%) as compared to group BL(63.33%). Other than arterial puncture which occurred in four patients(2 from either group), no adverse events were recorded.

DISCUSSION

The advantages of performing upper limb surgeries under brachial plexus block are many but the limited duration of action in prolonged surgeries is a significant drawback. When continuous catheter techniques are not available, adjuvants help by potentiating the action of local anaesthetics. The various adjuvants investigated include opioids, clonidine, dexamethasone, neostigmine, hyaluronidase and

bicarbonate.⁴⁻⁸

We evaluated the efficacy and safety of midazolam when combined with a mixture of bupivacaine and lignocaine for supraclavicular brachial plexus block. This was a prospective randomised study where the control group received a mixture of only local anaesthetics in the same volume and concentration as the study group. The onset time of sensory block was 2.37±1.54 min in the midazolam group as compared to 6.33±3.20 min in the control group. Our findings were in consonance with those of Jarbo, Batra et al where the onset of sensory block was 12 ± 2.9 min with midazolam as compared to 20 ± 3.8 min in the control group. Onset of block was faster in our study as we had used a combination of lignocaine and bupivacaine as compared to Jarbo, Batra et al¹⁵ who used only bupivacaine. Onset of motor block was 2.57±1.68 min in the midazolam group as compared to 7.33 ± 3.41 min in the control group. Similar results were found by Jarbo et al¹⁵ where the onset of motor block with addition of midazolam was 9.2 ±2.38 min as compared to 17.1±3.83 min with plain bupivacaine. This could be due to a local anaesthetic property of midazolam and its synergistic action with that of local anaesthetics.⁹⁻¹¹

In our study however, the onset of sensory block was faster as compared to motor block. This was in contrast to studies conducted by Winne et al¹⁶ and Jarbo Batra et al where the motor block preceded the onset of sensory block. A study was conducted by Winnie et al which studied separate onset and recovery of sensory and motor block in peripheral (mantle)and central (core) bundle within nerve trunks. Due to the somatotrophic configuration of nerve fibres in the trunks, motor block sets in earlier than sensory block. Motor fibres are located more peripherally than sensory fibres and hence a local anaesthetic injected peripherally will arrive at and begin to block motor fibres before it reaches the more centrally located sensory fibres.

The duration of sensory blockade (19.20±5.98 hr) was significantly longer (P <0.05) in the midazolam group as compared to the control group (14.6±6.04 hr). The duration of motor block was also significantly prolonged to 9.40±3.02hours when midazolam was added as compared to 6.87±2.45 hours with only local anaesthetics. Prolongation of motor block may be undesirable in surgeries of short duration.

We noted a longer duration of both sensory and motor block as compared to the study by Jarbo Batra et al. This was probably because we used an adrenalized solution of local anaesthetics in both groups. Our results show that sensory block tended to last longer as compared to motor block which is similar to the observation by Winnie et al and Jarbo Batra et al. These authors explained that large fibres require higher concentration of local anaesthetics than small fibres.

Time	Group BLM				Group BL				Mann-whitney U test	P Value
	Mean	SD	Median	IQR	Mean	SD	Median	IQR		
0min	6.47	1.85	7.00	2.00	6.83	1.44	7.00	2.00	400	0.460
2 min	4.13	1.59	4.00	2.00	6.30	1.26	6.50	2.00	127	<0.01
5 min	1.23	1.59	1.00	2.00	4.97	1.47	5.00	2.00	54	<0.01
10 min	0.00	0.00	0.00	0.00	1.60	2.08	0.00	3.00	255	<0.01
20 min	0.00	0.00	0.00	0.00	0.17	0.59	0.00	0.00	405	0.506
30 min	0.00	0.00	0.00	0.00	0.10	0.40	0.00	0.00	420	0.657
1 hr	0.00	0.00	0.00	0.00	0.07	0.25	0.00	0.00	420	0.657
2 hr	0.00	0.00	0.00	0.00	0.07	0.25	0.00	0.00	420	0.657
6 hr	0.20	0.66	0.00	0.00	3.33	2.28	4.00	3.00	122	<0.01
12 hr	2.90	1.35	3.00	2.00	5.47	1.11	6.00	1.00	69	<0.01
24 hr	4.20	0.76	4.00	1.00	5.90	0.99	6.00	2.00	94	<0.01

Table-3: Peri-operative Pain Scores using Visual Analogue Scale

The minimal effective concentration of local anaesthetics for large motor fibres is greater than for small (sensory) fibres.¹⁷ Postoperatively significantly lower pain scores were recorded at 6 hr, 12 hr and 24 hr with addition of midazolam which could be due to its antinociceptive action on GABA-A receptors present in the brachial plexus. Bhisitkul et al¹³ showed that axonal GABA receptors are present on both normal and regenerated sensory fibres in rat peripheral nerve. It was Cairns et al who discovered that activation of GABA receptors within the temporomandibular joint could diminish the conduction of nociceptive signal transmission.¹⁴ The Ramsay sedation score was comparable between the two groups and the highest score recorded was 2. The study conducted by Jarbo Batra et al showed higher sedation scores with midazolam 15 min after injecting the drug until 30 min postoperatively. The sedative effects of midazolam are observed due to partial vascular uptake of the drug and its transfer to the central nervous system. Midazolam is highly lipophilic and diffuses faster in to the blood vessels. It has a rapid clearance (6-11 ml/kg/min) and short half life (1.7 – 2.6hr)¹⁸

Similar to other studies we did not find any significant difference in the pulse rate, systolic and diastolic blood pressure and arterial oxygen saturation intra-operatively and until 24 hr post-operatively. When midazolam is added in doses of about 1- 2 mg intrathecally has a positive effect on perioperative and chronic pain. Intrathecal midazolam has not been associated with neurotoxic problems in animals.¹⁹ Tucker et al found that midazolam given intrathecally potentiates the analgesic effect of intrathecal fentanyl in labouring patients²⁰

We studied midazolam at a dose of 50mcg/kg as others have used the same doses for neuraxial blocks and have not observed any serious consequences. The average dose we used was 2.5mg to 3 mg. Trivedi V, Patel N²¹ compared the sedation scores of 5mg of midazolam with that of 150mcg of clonidine in combination with local anaesthetics in supraclavicular brachial plexus block. They concluded that Clonidine provides better postoperative analgesia and more sedation than midazolam. Kim Min Soo et al²² compared the effects of fentanyl 100 mcg versus 3 mg midazolam versus a combination of 3 mg midazolam + 100 mcg fentanyl added to local anaesthetics (40 ml of 1.5% lignocaine). They concluded that incidence of successful block was higher

when a combination of midazolam and fentanyl was added. Hayes et al²³ found that the group which received 50mcg/kg midazolam intra-articularly in combination with 0.25% bupivacaine (20ml) had significantly lower VAS at rest and during movement as compared to the group receiving 50mcg/kg midazolam in normal saline(20ml) and the group given only 0.25% bupivacaine(20ml).

CONCLUSION

We conclude that midazolam in the dose of 50mcg/kg can be safely used to potentiate the action of local anaesthetics in brachial plexus block.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 27-03-2016; **Published online:** 30-04-2016