Original Research Article

A comparative study of brachial plexus block using bupivacaine with midazolam and bupivacaine alone in upper limb surgeries

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Abstract

Background: Adjuncts to local anaesthetics for brachial plexus block may enhance the quality and duration of analgesia. Midazolam, a water-soluble benzodiazepine, is known to produce antinociception and enhance the effect of local anaesthetics when given epidurally or intrathecally.
Aim: Study was to assess the effect of Midazolam added to brachial plexus block by supraclavicular approach.
Materials and methods: A prospective, randomized, single blinded study was conducted on 100 ASA Grade I or II adult patients undergoing upper limb surgeries under supraclavicular brachial plexus block. Patients were randomly divided into two groups. Patients in Group B (n = 50) Bupivacaine and Group BM (n = 50) Bupivacaine with Midazolam. The onset time and duration of sensory and motor blockade were recorded. Hemodynamic variables (i.e., heart rate, blood pressure and oxygen saturation), sedation scores and rescue analgesic requirements were recorded for 24 hour postoperatively.
Results: The onset of sensory and motor block was significantly faster in Group BM compared to Group B ($p < 0.05$). The duration of sensory and motor block was significantly longer in Group BM compared to Group B ($p < 0.05$). Rescue analgesic requirements were significantly less in Group BM compared to Group B ($p < 0.05$). Hemodynamics and sedation scores did not differ between the two

groups in the post-operative period.
Conclusion: Midazolam (0.05 mg/kg) in combination with 30 mL of Bupivacaine (0.375%) hastened onset of sensory and motor block, and improved postoperative analgesia when used in brachial plexus block, without producing any adverse events.

Key words

Brachial plexus block, Bupivacaine, Midazolam, Upper limb surgeries.

Introduction

Brachial plexus block provides a useful alternative to general anaesthesia for upper limb surgeries. They achieve near-ideal operating conditions by producing complete muscular relaxation, maintaining stable intra-operative hemodynamics and the associated sympathetic block. The sympathetic block decreases postoperative pain, vasospasm and edema. Of various local anaesthetics, Bupivacaine is used most frequently, as it has a long duration of action varying from 3 to 8 hours [1-4]. However there are many limiting factors like delayed onset, patchy or incomplete analgesia, sometimes short duration etc. Various drugs like Neostigmine, Opioids, Hyaluronidase, and Clonidine etc. [1-4] have been added to local anaesthetics in order to modify the block in terms of quick onset, good quality, prolonged duration and post-operative analgesia. But these are not without adverse systemic effects or of doubtful efficacy. Midazolam, a water-soluble benzodiazepine is known to produce antinociception and to enhance the effect of local anaesthetic when given epidurally or intrathecally. Midazolam produces this effect by its action on Gamma Amino Butyric Acid-A (GABA-A) receptors. GABA receptors have also been found in peripheral nerves. So the present study is being undertaken in a randomized single blinded manner to evaluate the onset time and analgesic efficacy of Midazolam- Bupivacaine combination compared to plain Bupivacaine (0.375%) for brachial plexus block by supraclavicular approach.

Materials and methods

This study was conducted on 100 patients undergoing upper limb surgeries aged between 15 to 55 years under supraclavicular block in Osmania General Hospital, attached to Osmania Medical College, Hyderabad between November 2013 and October 2015. Informed written consent was taken. Results were recorded using a pre-set proforma.

Inclusion criteria

ASA Class I and II, aged between 15 to 55 years, systolic blood pressure of 100 to 139 mm of Hg, diastolic blood pressure of 60 to 89 mm of Hg.

Exclusion criteria

Patient refusal, known cause of hypersensitive reaction to midazolam or bupivacaine, patients with medical complications like severe hypovolemia, shock, septicaemia etc., patients with abnormal coagulation profile, local infection at the site of proposed puncture of supraclavicular block.

Investigations required are Hemoglobin (Hb%), Total Leukocyte Count (TLC), Differential Leukocyte Count(DLC), Bleeding Time (BT), Clotting Time(CT), Random Blood Sugar(RBS), Blood urea and Serum Creatinine ,ECG ,HIV, HBs Ag. Written informed consent, intravenous access to a 20 guage IV cannula on the contralateral upper limb under aseptic techniques was done.

Procedure

A prospective, randomized, single blinded study was undertaken. 100 patients posted for upper limb surgeries under supraclavicular block were assigned to 2 groups, each containing 50 patients.

Control group – Group-B: received 30 ml Bupivacaine (0.375%),
Study group – Group BM: received 30 ml of

mixture of Bupivacaine (0.375%) and Midazolam (0.05 mg/kg).

Patients lay supine, arms by the side and head turned slightly to the other side, The interscalene groove and mid-point of clavicle were identified, After aseptic preparation of the area, at a point 1.5 to 2.0 cm posterior and cephalad to mid-point of clavicle, subclavian artery pulsations are felt. A skin wheal was raised with local anaesthetic just cephalo-posterior to the pulsations, Next, a 22 gauge, 5 cm needle, mounted on a 20 ml syringe, was passed through the same point, parallel to the head and neck, in a caudad, slightly medial and posterior direction, until either paraesthesia was elicited or first rib was encountered, If the first rib was encountered, the needle would be moved over the first rib until a paraesthesia was elicited either in the hand or arm, After eliciting paraesthesia the study medication was injected, All patients were monitored for anaesthesia and analgesia upto 24 hours post-operatively, Sensory block was evaluated by temperature testing using spirit soaked cotton on skin dermatomes C_4 to T_2 whereas motor block was assessed by asking the patient to adduct the shoulder and flex the fore-arm against gravity, Onset of sensory block was defined as the time elapsed between injection of drug and complete loss of cold perception of the hand, while onset of motor blockade was defined as the time elapsed from injection of drug to inability to adduct arm and flex fore arm against gravity (inability to touch one's nose), Sedation score described by Culebras et al[4] was used to assess sedation.

Culebras, et al. sedation score:

1 – awake and alert,
2 – sedated, responding to verbal stimulus,
3 – sedated, responding to mild physical stimulus,
4 – sedated, responding to moderate or severe physical stimulus,
5 – not arousable.

Heart rate, non-invasive blood pressure and O_2 saturation were also monitored. Duration of sensory block (the time elapsed between injection of drug and appearance of pain requiring analgesia) and duration of motor block (the time elapsed between injection of drug and complete return of muscle power) would also be recorded. IM injection of Diclofenac sodium was given as rescue analgesic when patient complains of pain. Number of rescue analgesics needed in 24 hours of post-operative period was also recorded. Quantitative data was analysed by student's 't' test. Qualitative data was analysed by Chi-square test. A *p* value of < 0.05 was considered statistically significant.

Results

Hundred ASA Gr I and II of either sex aged between 15-55 years, posted for upper limb surgeries under supraclavicular brachial plexus block were selected for the study. The study was undertaken to evaluate the efficacy of Midazolam (0.05mg/kg) as an adjuvant to Bupivacaine (0.375%) in comparison with plain Bupivacaine (0.375%) for brachial plexus block by supraclavicular approach.

The minimum age of the patient was 15 years and the maximum age was 55 years as per **Table - 1**. The mean age of the patients in group BM was 32.3 ± 10.51 and in group B was 34.3 ± 11.89 years. Age distribution between two groups was comparable. The mean time for onset of sensory block in group BM was 12.3 ± 1.35 min and in group B was 19.08 ± 1.7 min. The statistical analysis by student's unpaired 't' test showed that, the time for onset of sensory block in group BM was significantly faster when compared to group B ($p< 0.05$). The mean time for onset of motor block in group BM was 9.52 ± 1.37 min and in group B was 15.3 ± 2.09 min. The statistical analysis by unpaired student's 't' test showed that, the time for onset of motor block was significantly faster when compared to group B ($p< 0.05$). Patients of both groups were observed for 24 hours. Time was noted when the patient asked for rescue analgesics. The mean duration of sensory block in group BM was 13.65 ± 2.01 hours and in group B was 6.87 ±

0.89 hours. The statistical analysis by students unpaired 't' test showed that the duration of sensory block in group BM was significantly longer when compared to group B ($p < 0.05$). The mean duration of motor block in group BM was 7.23 ± 1.01 hours and the group B was 6.17 ± 0.77 hours. The statistical analysis by students't' test shows significant difference, with p value less than 0.05 ($p < 0.05$).

Table – 1: Study Details.

Age Distribution (Age in years)	**Mean ± SD**	**p value**	**Significance**
Bupivacaine	34.3 ± 11.89	0.375	Not Sig
Bupivacaine+Midazolam	32.3 ± 10.51		
Time for onset of sensory block (min)			
Bupivacaine	19.08 ± 1.7	< 0.001	HS
Bupivacaine+Midazolam	12.3 ± 1.35		
Time for onset of motor block (min)			
Bupivacaine	15.30 ± 2.09	< 0.001	HS
Bupivacaine+Midazolam	9.52 ± 1.37		
Duration of sensory block (hrs)			
Bupivacaine	6.87 ± 0.89	< 0.001	HS
Bupivacaine+Midazolam	13.65 ± 2.01		
Duration of motor block (hrs)			
Bupivacaine	6.17 ± 0.77		
Bupivacaine+Midazolam	7.23 ± 1.01	< 0.001	HS

(HS- Highly significant, SS- statistically significant)

In group B, all patients were awake and alert and had sedation score of 1. In group BM, sedation corresponding to score 2 was observed in some patients between 15 min from time of injection and 60 min. 20% of patients at 15 min, 32% of patients at 30 min and 26% of patients at 60 min had sedation score of 2. None of the patients had sedation score of 3 and above during the study period. Statistical analysis of sedation score by chi-square test showed that the difference in sedation score was significant ($P < 0.05$) as per **Table - 2**.

In group B, the mean pulse rate ranged from 76 ± 6.2 to 77 ± 6.8 beats / min. In group BM, the mean pulse rate ranged from 74 ± 6.1 to 76 ± 6.7 beats / min. The statistical analysis by student's unpaired 't' test showed that there was no significant difference in pulse rate between the two groups ($p > 0.05$). In group B, the mean diastolic blood pressure ranged from 75 ± 6.6 to 77 ± 7.4 mm of Hg. In group BM, DBP ranged from 75 ± 7.11 to 76 ± 7.59 mm of Hg. The statistical analysis by unpaired student's 't' test showed that there was no significant difference in systolic blood pressure between two groups ($p > 0.05$). In group B, the mean O_2 saturation ranged from 99.7 ± 0.57% to 99.8 ± 0.51%. In group BM, the mean O_2 saturation ranged from 98 ± 0.5%. The statistical analysis by students unpaired't' test showed that there was no significant difference in O_2 saturation between the two groups ($p > 0.05$) as per **Table - 3**.

In group BM, 74% patients required only 1 rescue analgesic dosage and 26% of patients required 2 rescue analgesic doses in post-op 24 hours. In group B 76% of patients required 2 and 24% of patients required 3 rescue analgesic doses in post-op 24 hours. This difference in number of rescue analgesic doses required by patient of both groups is statistically significant by chi-square test ($\chi^2 = 61.25$, $P < 0.05$) as per **Table - 4**.

Table - 2: Shows Sedation score.

Time of Assessment	Scores *	Bupivacaine	Bupivacaine - Midazolam	X2 Value, Significance
0 min	1	50 (100)	50 (100)	-
	2	0	0	No Difference
5 min	1	50 (100)	50 (100)	-
	2	0	0	No Difference
15 min	1	50 (100)	40 (80)	$X^2 = 9.0$
	2	0	10 (20)	P<0.05 Sig
30 min	1	50 (100)	34 (68)	X2 = 16.74
	2	0	16 (32)	P<0.05 Sig
60 min	1	50 (100)	37 (74)	X2 = 12.73
	2	0	13 (26)	P<0.05 Sig
2 hrs	1	50 (100)	50 (100)	-
	2	0	0	No Difference
6 hrs	1	50 (100)	50 (100)	-
	2	0	0	No Difference
12 hrs	1	50 (100)	50 (100)	-
	2	0	0	No Difference
24 hrs	1	50 (100)	50 (100)	-
	2	0	0	No Difference

(1 – Aware and alert, 2 – Sedated responding to verbal stimulus, 3 – Sedated, responding to mild physical stimulus, 4 – Sedated, respond to moderate to severe physical stimulus, 5 – Not arousable)

Discussion

Brachial plexus block provides postoperative analgesia of short duration, even when a long-acting local anaesthetic like Bupivacaine is used alone. Various adjuvant drugs like Opioids, Clonidine, Neostigmine and Hyaluronidase have been evaluated in conjunction with local anaesthetics to prolong the period of analgesia, but they were found to be either ineffective or to produce an unacceptably high incidence of adverse effects. Midazolam a water soluble benzodiazepine is known to produce antinociception and to enhance the effect of local anaesthetic when administered intrathecally and epidurally. Midazolam produces this effect by its action on GABA receptors. GABA receptors are also found in peripheral nerves. Hence an attempt has been made to assess the efficacy of Midazolam as an adjuvant to Bupivacaine (0.375%) in brachial plexus block (supraclavicular approach) in terms onset time, duration of analgesia and sedation. Haemodynamic variables and rescue analgesic requirements in first 24 hours were also studied. A total of 100 patients within the age group of 15-55 were in included in the study, 50 in each group. Out of which the mean age of group B (receiving only Bupivacaine) was 34.3 ± 11.89 years and the mean age of group BM (receiving Midazolam with Bupivacaine) was 32.3 ± 10.51 years. Hence both groups were comparable in regard to age. Male to female ratio was almost same. In our study we found that the onset of sensory and motor blocks was significantly faster in patients who received a combination of Midazolam and Bupivacaine. Onset of sensory block was 12.3 ± 1.5 min in group BM; and 19.08 ± 1.7 min in group B. Onset of motor block was 9.52 ± 1.37 min in group BM and 15.30 ± 2.09 min in group B. This could be due to a local anaesthetic property of Midazolam and its synergistic action with local anaesthetics. The onset of motor block was found to be faster than the onset of sensory block in both groups.

Winnie, et al. [5], observed this also, and attributed this to the somatotrophic arrangement of fibres in a nerve bundle at the level of the trunks in which motor fibres are located more peripherally than sensory fibres. Hence, a local anaesthetic injected perineurally will begin to block motor fibres before it arrives at the centrally located sensory fibres. Our results showed that sensory block tended to last longer as compared to motor block which agrees with the observation by de Jong, et al. [6]. These authors explained that large fibres require a higher concentration of local anaesthetic than small fibres. The minimal effective concentration of local anaesthetic for large (motor) fibres is greater than for small (sensory) fibres. Thus, motor function return before pain perception and duration of motor block is shorter than the sensory block [6]. In our study duration of motor blocks were different between the groups. (Group BM, 7.23 ± 1.01 hrs; group B, 6.17 ± 0.77 hrs). In our study, the mean duration of sensory block (i.e. time elapsed from time of injection to appearance of pain requiring analgesia) was significantly higher ($p < 0.05$) in group BM than in group B. (group BM, 13.65 ± 2.01 hrs; group B, 6.87 ± 0.89 hrs). A study was conducted by Koj Jarbo, YK Batra and NB Panda to assess the efficacy of Midazolam as an adjuvant to Bupivacaine in brachial plexus block. 40 ASA I or II patients undergoing upper limb surgery under supraclavicular brachial plexus block were allocated into two groups. Group B received 30ml of 0.5% Bupivacaine Group BM received 30ml of 0.5% Bupivacaine with 0.05mg/kg of Midazolam. The mean onset of sensory block (group BM, 12 ± 2.9 min, group B, 20 ± 3.8 min) and motor block (group BM, 9.2 ± 2.38 min; group B, 17.1 ± 3.83 min) was significantly faster in group BM than in group B ($P < 0.05$). The duration of sensory block (group BM, 7 ± 4.32 hr; group B, 5.95 ± 1.4 hr) was also longer in group BM than in group B. the duration of motor block was not different between the groups (group BM, 5.65 ± 3.32 hr, group B, 5.1 ± 1.14 hr). These values are comparable with our study except for the duration of motor block which was also significantly longer in our study. Various studies in which Midazolam was used in central neuraxial block found that Midazolam with Bupivacaine improves analgesic characteristics compared to Bupivacaine alone.

Gulec, et al. [7], found that a Bupivacaine and Midazolam combination prolonged postoperative analgesia compared to a Bupivacaine – Morphine combination when administered caudally. Nishiyama, et al., added Midazolam to a continuous epidural infusion of Bupivacaine and observed improved analgesia. Batra, et al., used Bupivacaine with Midazolam intrathecally and found a significantly lower visual analogue score compared to Bupivacaine alone. Midazolam produces this additive effect on local anaesthetics by its action on the GABA-A receptor complexes present in the spinal cord. The addition of Midazolam in doses of approximately 1 to 2 mg intrathecally has a positive effect on perioperative and chronic pain therapy [8]. Studies in animals have revealed no neurotoxic effects of intrathecally administered Midazolam [9-11]. More recently, Tucker and associates demonstrated that administration of intrathecal Midazolam causes potentiation of the analgesic effect of intrathecal Fentanyl in labouring patients. The administration of intrathecal Midazolam, 2 mg, did not increase the occurrence of neurologic or urologic symptoms [12]. In our study, the number of patients who required rescue analgesia and the mean number of supplemental analgesic boluses required were also significantly lower in patients in Group BM.

Similar observation was made in the above mentioned study by Koj Jarbo, YK Batra and NB Panda. The prolonged analgesia in Group BM could be due to the action of Midazolam on GABA-A receptors present in the brachial plexus and thus producing antinociception. Various authors have demonstrated the presence of GABA receptors in peripheral nerves. Brown and Marsh demonstrated GABA receptors in mammalian peripheral nerve trunk. Bhisitkul, et al., showed that axonal GABA receptors are

present on both normal and regenerated sensory fibres in rat peripheral nerve. Cairns, et al., observed the presence of GABA receptors within the temporomandibular joint and that its activation could decrease the transmission of nociceptive signals. The action of Midazolam on GABA receptors is well established.

Table - 3: Hemodynamic variables in study.

Time of Assessment	Mean+/- SD		P Value	Significance
	Bupivacaine	Bupivacaine -Midazolam		
Pulse Rate (beats / min)				
0 min	77 ± 6.8	75 ± 6.6	>0.05	NS
5 min	77 ± 6.6	76 ± 6.7	>0.05	NS
15 min	76 ± 6.5	76 ± 6.4	>0.05	NS
30 min	76 ± 6.8	76 ± 6.7	>0.05	NS
60 min	76 ± 6.6	75 ± 6.2	>0.05	NS
2 hrs	77 ± 6.5	75 ± 5.6	>0.05	NS
6 hrs	77 ± 6.4	76 ± 5.6	>0.05	NS
12 hrs	76 ± 6.2	74 ± 6.1	>0.05	NS
24 hrs	77 ± 6.5	76 ± 7.8	>0.05	NS
Systolic blood pressure (mm of Hg)				
0 min	117 ± 9.9	118 ± 9.5	>0.05	NS
5 min	118 ± 10.1	117 ± 10.5	>0.05	NS
15 min	118 ± 10.1	118 ± 10.3	>0.05	NS
30 min	118 ± 10.3	118 ± 9.9	>0.05	NS
60 min	118 ± 9.9	117 ± 9.7	>0.05	NS
2 hrs	118 ± 9.6	117 ± 9.7	>0.05	NS
6 hrs	116 ± 9.3	118 ± 9.6	>0.05	NS
12 hrs	117 ± 9.8	116 ± 10.0	>0.05	NS
24 hrs	117 ± 9.4	116 ± 9.4	>0.05	NS
Diastolic blood pressure (mm of Hg)				
0 min	76 ± 7.71	75 ± 7.11	>0.05	NS
5 min	76 ±7.56	76± 7.59	>0.05	NS
15 min	76 ± 7.21	76± 7.31	>0.05	NS
30 min	75 ± 6.59	76 ± 7.18	>0.05	NS
60 min	77 ± 7.29	76 ± 7.42	>0.05	NS
2 hrs	77 ± 7.40	76 ± 7.58	>0.05	NS
6 hrs	76 ± 7.33	76 ± 7.39	>0.05	NS
12 hrs	76 ± 7.75	76 ± 7.83	>0.05	NS
24 hrs	76 ± 6.87	76 ± 6.93	>0.05	NS
Oxygen saturation (%)				
0 min	99.7 ± 0.57	99.7 ± 0.59	>0.05	NS
5 min	99.8 ± 0.51	99.7 ± 0.54	>0.05	NS
15 min	99.7 ± 0.63	99.7 ± 0.65	>0.05	NS
30 min	99.7 ± 0.65	99.8 ± 0.53	>0.05	NS
60 min	99.7 ± 0.58	99.8 ± 0.4	>0.05	NS
2 hrs	99.7 ± 0.64	99.8 ± 0.48	>0.05	NS
6 hrs	99.7 ± 0.56	99.8 ± 0.47	>0.05	NS
12 hrs	99.7 ± 0.75	99.8 ± 0.55	>0.05	NS
24 hrs	99.7 ± 0.53	99.8 ± 0.53	>0.05	NS

Table - 4: Number of rescue analgesics in post-op 24 hours.

No. of rescue analgesics in 24 hours post-op	Bupivacaine	Bupivacaine + Midazolam
1	0	37 (74)
2	38 (76)	13 (26)
3	12 (24)	0

$\chi^2 = 61.25$ $p < 0.0001$ Highly Significant

We studied Midazolam at a dose of 0.05 mg/kg, as others have used the same dosage in central neuraxial block without any significant adverse effects. In our study, sedation scores were higher in patients in Group BM compared to Group B, 15 min after injecting the drug until 60 min after injection. Similar observation was made in the above mentioned study by Koj Jarbo, YK Batra and NB Panda. This may have been due to partial vascular uptake of Midazolam, and its transport to the central nervous system where it acts and produces sedation. The limited duration of sedation could be explained by the fact that Midazolam is highly lipophilic and diffuses faster into the blood vessels, by its rapid clearance (6-11 mL/kg/min) and short half-life (1.7-2.6 hr). Though mean sedation score in group BM was higher as compared to group B ($P < 0.05$), we did not observe clinically significant sedation in patients in group BM in postoperative period. No patient experienced airway compromise or required airway assistance. This mild sedation was actually desirable during intra-operative period.

Conclusion

In conclusion, Midazolam 0.05 mg/kg when added to 30 ml of 0.375% Bupivacaine for supraclavicular brachial plexus block, speeds the onset of sensory and motor blocks ($p < 0.05$). The combination produces improved analgesia, resulting in a prolonged effect and reduced requirements for rescue analgesics and it has following effects faster onset of sensory block, faster onset of motor block, longer duration of sensory and motor blocks , less number of rescue analgesics in post-op 24 hours , comfortable sedation intraoperatively without any need for airway assistance , no significant difference in haemodynamic variables i.e., pulse rate, Systolic Blood Pressure, Diastolic Blood Pressure and O_2 saturation.

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