Original Research Article

A clinical comparison between bupivacaine midazolam combination and bupivacaine plain in brachial plexus block by supraclavicular approach

Jagadish Chandra Mishra[1*], Pradip Kumar Maharana[2]

[1]Associate Professor, [2]Assistant Professor
Kalinga Institute of Medical Sciences (KIMS), KIIT University, Bhubaneswar, Odisha, India
[*]Corresponding author email: **mishrajccb@gmail.com**

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Abstract

Background: The study is to describe the efficacy of Midazolam when used with Bupivacaine as local anesthetic in Supraclavicular brachial plexus block. The focus will be on the onset and analgesic duration of nerve blocks along with any neurotoxic concerns or neuroprotective potential.

Materials and methods: A prospective, randomised single blinded study was undertaken in 100 patients posted for upper limb surgeries under supraclavicular brachial plexus block and were assigned into 2 groups, each containing 50 patients.

- Control group – Group B: received 30ml Bupivacaine 0.375%
- Study group – Group BM: received 30ml of mixture of Bupivacaine 0.375% and Midazolam 0.05mg/kg.

Results: The onset of sensory and motor block was significantly faster in group BM compare 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 groups in the postoperative period.

Conclusion: Midazolam 0.05mg/kg when addded to 30ml of Bupivacaine 0.375% 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.

Key words

Bupivacaine, Midazolam, Post-operative analgesia, Supraclavicular brachial plexus block, Upper limb surgeries.

Introduction

Peripheral Nerve blocks have become an alternative to General anesthesia has become a standard practice through the world. Percutaneous supraclavicular brachial plexus blockade was introduced in clinical practice by Kulenkampff in 1911. Brachial plexus block is often called "spinal anesthesia of the upper extremity "because of rapid onset, predictable and complete anaesthesia and ubiquitous use in all upper limb surgeries. Block is performed at the level of distal trunks and origin of divisions, where brachial plexus is confined to its smallest surface area on first rib. The three trunks carry entire sensory, motor, and sympathetic innervations of upper extremity, with exception of uppermost part of medial side of arm (T2).

Reasons for high success rate are [1]

- Anatomic characteristics.
- Relatively easy to perform.
- Analgesic and opioid sparing effect.
- Provides good quality analgesia with stable intraoperative hemodynamics and a smooth transition into postoperative period.
- Avoidance of polypharmacy and undesirable side effects of general anesthesia.
- Associated sympathetic block decreases postoperative pain, vasospasm and edema.
- Early resumption of oral feeding, ambulation and reduced hospital stay.
- Decreased postoperative pulmonary, gastrointestinal and thromboembolic complications

Brachial plexus blocks provide a useful alternative to general anesthesia for upper limb surgeries. They achieve near ideal operating conditions by producing complete muscular relaxation. Intraoperative hemodynamics are better maintained and the associated sympathetic block decreases vasospasm, edema and post-operative pain.

Supraclavicular technique is commonly used for surgeries on the forearm and hand. This block which provides faster 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].

Bupivacaine is used most frequently, as it has a long duration of action varying from 3 to 8 hours. The onset of motor block was found to be faster than the onset of sensory block in both groups. Winnie, et al., 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 [3]. Bupivacaine has a long duration of action among the local anesthetic agents. Its action have been prolonged by adding epinephrine, neostigmine, opioids, hyaluronidase, clonidine, dexmedetomidine and dexamethasone. Midazolam, a water-soluble benzodiazepine, is known to produce antinociception Midazolam a water soluble benzodiazepine is known to produce antinociception and to enhance the effect of local anesthetic when given epidurally or intrathecally. Midazolam produces this effect by its action on gamma amino butyric acid A receptors. GABA receptors have also been found in peripheral nerves.

Adjuvants have been added to bupivacaine in brachial plexus blocks to prolong the duration of analgesia but they have been found to be either ineffective or to produce an unacceptably high incidence of adverse effects.

So the present study is being undertaken in a randomised 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.

Aim

In this study, an effort is made to describe the efficiency of Midazolam along with Bupivacaine as local anesthetic in supraclavicular brachial plexus block on the onset and analgesic duration of nerve blocks along with any neurotoxic or neuroprotective potentials.

The present study was undertaken to compare the effectiveness of adding Midazolam 0.05 mg/kg to Bupivacaine 0.375% in supraclavicularbrachial plexus block for upper limb surgeries with plain Bupivacaine 0.375%.

Following parameters are studied:

- Onset of sensory and motor blockade.
- Duration of sensory and motor blockade.
- Sedation score intrathecal and postoperatively.
- Hemodynamic variables (HR, BP, O_2 saturation).
- Number of rescue analgesics in postoperative 24 hours.

Materials and methods

This study was conducted on 100 patients undergoing upper limb surgeries aged between 15-55 years of ASA 1 and 2 under supraclavicular brachial plexus block in medical sciences, between November 2014 – October 2016. Informed written consent was taken. Result values were recorded using a preset proforma. Routine investigations were ordered.

A prospective, randomised single blinded study was undertaken in 100 patients posted for upper limb surgeries under supraclavicular brachial plexus block and were assigned into 2 groups, each containing 50 patients.

- Control group – Group B: received 30ml Bupivacaine 0.375%
- Study group – Group BM: received 30ml of mixture of Bupivacaine 0.375% & Midazolam 0.05 mg/kg.

After eliciting paraesthesia and negative aspiration of blood, the study medication was injected. All patients were monitored for anesthesia and analgesia up to 24 hours postoperatively.

Sensory block was evaluated by temperature testing using spirit soaked cotton on skin dermatomes C4 – T2, whereas motor block was assessed by asking the patient to addict the shoulder and flex the forearm 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 eas defined as the time elapsed from injection of drug to complete motor block.

Sedation score described by Culebras, et al. [4] was used to assess sedation.
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 oxygen 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) was also recorded. Intramuscular injection of Diclofenac sodium was given as rescue analgesic when patient complains of pain and number of rescue analgesics in 24 hours postoperative period was also recorded.

Statistical analysis

Quantitative data was analysed by students t test. Qualitative data was analysed by Chi-square test. P value <0.05 would be considered statistically significant.

Results

Results were depicted as per **Table – 1** to **Table – 11**.

Table – 1: Age distribution of study groups.

Study groups	Mean ± SD
Bupivacaine	33.4 ± 10.81
Bupivacaine + Midazolam	32.9 ± 12.32

T value = 0.216, P value = P > 0.05 not significant

Table – 2: Time for onset of sensory block (min).

Study groups	Onset time (min)
Bupivacaine	19.08 ± 1.7
Bupivacaine + Midazolam	11.26 ± 1.5

Mean difference = 7.82, T value = 24.13, P value = P < 0.001 highly significant

Table – 3: Time for onset of motor block (min).

Study groups	Onset time (min)
Bupivacaine	15.30 ± 2.09
Bupivacaine + Midazolam	9.56 ± 1.32

Mean difference = 5.74, T value = 16.38, P value = P < 0.001 highly significant

Table – 4: Duration of sensory block (hours).

Study group	Duration of block (hours)
Bupivacaine	5.84 ± 0.49
Bupivacaine + Midazolam	13.81 ± 1.23

Mean difference = 7.96, T value = 42.2, P value = P < 0.001 highly significant.

Table – 5: Duration of motor block (hours).

Study group	Duration of block (hours)
Bupivacaine	5.13 ± 0.45
Bupivacaine + Midazolam	5.25 ± 0.45

Mean difference = 0.12, T value = 1.32, P value = P > 0.05 not significant.

Table – 6: Number of rescue analgesics in postoperative 24 hours.

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

x2 = 61.25 , P < 0.0001 highly significant.

Discussion

Brachial plexus block provides postoperative analgesia for short duration, even when a long acting local anesthetic like bupivacaine is used alone. Various adjuvant drugs like opioids, clonidine, neostigmine and hyaluronidase have been evaluated in conjunction with local anesthetics 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 produces this effect by its action on gamma amino butyric acid-A (GABA-A) receptors which have also been found in peripheral nerves. Bhisitkul, et al. 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 [2].

Midazolam enhance the affinity of the receptors for GABA (Collins, 1993). As a result of this drug- induced increased affinity of GABA receptors for the inhibitory neurotransmitter, an enhanced opening of chloride gating channels results in increased chloride conductance, thus producing hyperpolarization of the postsynaptic cell membrane [5].

Hence an attempt has been made to assess the efficacy of Midazolam as an adjuvant to Bupivacaine (0.375%) in brachial plexus block by supraclavicular approach in terms of onset time, duration of analgesia and sedation.

Hemodynamic variables and rescue analgesic requirements in first 24 hours was also studied.

A total of 100 patients within age group of 15-55yrs were included in the study, 50 in each group. Out of which the mean age of group B receiving only Bupivacaine was 33.4± 10.81 years and the mean age group of BM receiving Midazolam with Bupivacaine was 32.9 - 12.32 years. Hence both groups were comparable in regard to age. Male to female ratio was almost same.

Table – 7: 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)	x2 = 9.0
	2	0	10 (20)	P<0.05 significant
30 min	1	50 (100)	34 (68)	x2 = 16.74
	2	0	16 (32)	P<0.05 significant
60 min	1	50 (100)	37 (74)	x2 = 12.73
	2	0	13 (26)	P<0.05 significant
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

Table – 8: Pulse rate (beats/min).

Time of assessment	Mean ± SD Bupivacaine	Bupi + Midaz	Mean difference	T value	P value	Significance
0 min	77± 6.8	78± 7.4	1.48	1.03	P > 0.05	Not significant
5 min	77± 6.6	78± 7.0	1.24	0.91	P > 0.05	Not significant
15 min	76± 7.0	78± 7.0	1.44	1.03	P > 0.05	Not significant
30 min	76± 6.6	78± 7.4	1.46	1.04	P > 0.05	Not significant
60 min	77± 6.5	78± 7.2	1.36	0.99	P > 0.05	Not significant
2 hrs	77± 7.0	78± 7.0	1.1	0.79	P > 0.05	Not significant
6 hrs	77± 6.6	78± 7.0	1.48	1.05	P > 0.05	Not significant
12 hrs	76 ± 6	78± 7.0	2.04	1.49	P > 0.05	Not significant
24 hrs	77± 7.0	78± 7.0	1.52	1.09	P > 0.05	Not significant

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 in group BM is 11.26± 1.5 min; group B is 19.08± 1.7 min. Onset of motor block in group

BM is 9.56± 1.32 min, group B is 15.30± 2.09 min.

This could be due to a local anesthetic propert of Midazolam and its synergistic action with that of local anesthetics. The onset of motor block was found to be faster than the onset of sensory block in both groups. Winnie, et al. [6] 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 anesthetic injected peri neurally will begin to block motor fibres before it arrives at centrally located sensory fibres.

Table – 9: Systolic blood pressure (mmHg).

Time of assessment	Mean ± SD Bupivacaine	Bupi + Midaz	Mean difference	T value	P value	Significance
0 min	117±10.45	117±10.53	0.76	0.36	P>0.05	Not significant
5 min	118± 10.37	117±10.88	0.1	0.047	P>0.05	Not significant
15 min	118±10.01	118±10.84	0.08	0.038	P>0.05	Not significant
30 min	118± 10.38	118±11.01	0.12	0.056	P>0.05	Not significant
60 min	118 ± 9.47	117±10.86	0.02	0.01	P>0.05	Not significant
2 hrs	117±10.04	118±10.99	0.7	0.33	P>0.05	Not significant
6 hrs	117±10.01	118±11.19	0.48	0.22	P>0.05	Not significant
12 hrs	117 ± 9.96	118±11.10	0.68	0.32	P>0.05	Not significant
24 hrs	117 ± 9.85	118±11.07	1.04	0.49	P>0.05	Not significant

Table – 10: Diastolic blood pressure (mmHg).

Time of assessment	Mean ± SD Bupivacaine	Bupi + Midaz	Mean difference	T value	P value	Significance
0 min	76±7.72	77± 6.8	0.38	0.26	P>0.05	Not significant
5 min	76±7.52	77±6.74	1.02	0.71	P > 0.05	Not significant
15 min	76±7.07	77± 6.72	1.14	0.82	P > 0.05	Not significant
30 min	77±7.10	77± 6.85	0.38	0.27	P > 0.05	Not significant
60 min	76±7.03	77± 6.66	0.74	0.54	P > 0.05	Not significant
2 hrs	76±7.06	77±6.82	0.48	0.34	P > 0.05	Not significant
6 hrs	76±7.15	77±6.73	0.52	0.37	P > 0.05	Not significant
12 hrs	76 ± 6.9	77± 6.92	0.52	0.37	P > 0.05	Not significant
24 hrs	76 ± 6.9	77± 6.67	0.5	0.36	P > 0.05	Not significant

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. [7]. These authors explained that large fibres require a higher concentration of local anesthetic than small fibres. The minimum effective concentration of local anesthetic 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.

However in our study duration of motor blocks were not different between the groups (Group BM, 5.25± 0.45 hours; group B, 5.13± 0.45 hours).

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 13.81± 1.23 hours; Group B 5.84± 0.49 hours)

A study was conducted by koj jarbo, YK Batra and NB panda [8] to assess the efficacy of Midazolam as an adjuvant to Bupivacaine in brachial plexus block in ASA 1 or 2 patients undergoing upper limb surgery under supraclavicular brachial plexus block. The findings in the study concurs with the findings of our study.

Table – 11: Oxygen saturation (%).

Time of assessment	Mean ± SD		T value	P value	Significance
	Bupivacaine	Bupi + Midaz			
0 min	99 ± 0.56	99 ± 0.49	0	P > 0.05	Not significant
5 min	99 ± 0.47	98 ± 0.50	1.8	P > 0.05	Not significant
15 min	99 ± 0.49	99 ± 0.50	0.39	P > 0.05	Not significant
30 min	98 ± 0.54	98 ± 0.50	2.09	P > 0.05	Not significant
60 min	99 ± 0.50	98 ± 0.50	0.19	P > 0.05	Not significant
2 hrs	99 ± 0.48	99 ± 0.47	0.2	P > 0.05	Not significant
6 hrs	99 ± 0.49	99 ± 0.47	2.45	P > 0.05	Not significant
12 hrs	99 ± 0.57	99 ± 0.46	2.09	P > 0.05	Not significant
24 hrs	99 ± 0.48	99 ± 0.46	3.58	P > 0.05	Not significant

Tucker [9] 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 2mg did not increase the occurrence of neurological or urologic symptoms.

In our study, the number of patients who required rescue analgesia and the mean number of supplemental analgesic blouses were also significantly lower in patients in Group BM. Similar observation was made in the above mentioned study by Koj jarbo, et al. [8]. 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. [10], showed that axonal GABA receptors are present on both normal and regenerated sensory fibres in rat peripheral nerve. Cairns, et al. [11], 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 establishes.

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 ourstudy, 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, et al. [8]. 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 lipophillic and diffuses faster into the blood vessels by its rapid clearance (6-11 ml/kg/min) and short half life (1.7-2.6 hour). 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. No patient experienced airway compromise or required airway assistance.this mild sedation was actually desirable during that period.

In the study conducted by Koj Jarbo, et al. [8] it was concluded that Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation were comparable between groups and did not change significantly in the intraoperative or postoperative period. No adverse events were encountered in either group of patients.

In the study conducted by Nasreen Laiq, et al. [12], it was concluded that the duration of Motor and Sensory blockade was prolonged when Midazolam added to Bupivacaine compared when Bupivacaine used alone.

Safiya I Shaikh, et al. [13] in his study Midazolam as an adjuvant in Supraclavicular brachial plexus block' concluded that duration of pain relief in group BM was significantly longer than in group B (805.04 ± 175.75 min vs 502.24 ± 52.68 min).

The above observation concurs with the study results of Sathish and Srinivasan, et al. [14]. Our observations were similar to the above stated studies.

Conclusion

We conclude that the addition of Midazolam 0.05 mg/kg as adjuvant to Bupivacaine 0.375% is faster onset of sensory block & faster onset of Motor block. Longer duration of sensory block. Less number of rescue analgesics in postop 24 hours. Comfortable sedation intraoperatively without any need for airway assistance. No significant difference in duration of motor block and Hemodynamic variables, PR,SBP,DBP and Oxygen saturation.

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