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A Comparative Study of Brachial Plexus Block Using Bupivacaine with Midazolam and Bupivacaine Alone in Upper Limb Surgeries

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Abstract

Introduction: Upper limb surgeries can be done under general anesthesia. However, using Brachial plexus block is a better alternative. This method provides good muscular relaxation and also maintains intra-operative hemodynamics at a stable level. *Aim of the study:* To study the effect of Midazolam added to brachial plexus block by supraclavicular approach. *Materials and methods:* This was a prospective, randomized, single blinded study. A total of 100ASA Grade I or II adult patients who underwent upper limb surgeries under supraclavicular brachial plexus block were studied. Patients were randomly allocated to two groups of 50 each. Patients in Group B received 30 mL of 0.375% Bupivacaine and Group BM received 30 mL of 0.375% Bupivacaine with preservative free Midazolam 0.05 mg/kg. The onset time and duration of sensory and motor blockade were noted. The patients were observed for 24 hours postoperatively for hemodynamic variables, sedation scores and rescue analgesic requirements. *Results:* Group BM showed significantly quicker onset of sensory and motor block than Group B ($p < 0.05$). Group BM also had significantly longer duration of sensory and motor block ($p < 0.05$). Group BM had significantly less requirements for rescue analgesia ($p < 0.05$). Both groups showed similar hemodynamics and sedation scores postoperatively. *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.

Keywords: Brachial plexus block; Bupivacaine; Midazolam; Anesthesia in upper limb surgeries.

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Introduction

Upper limb surgeries can be done under general anesthesia. However, using Brachial plexus block is a better alternative. This method provides good muscular relaxation and also maintains intraoperative hemodynamics at a stable level. In addition it also provides associated sympathetic block which helps in reducing postoperative pain, vasospasm and edema caused by different local anesthetic agents. Bupivacaine is preferred frequently due to its longer duration of action which can vary from 3 to 8 hours. Bupivacaine has a few limiting factors like delayed onset, patchy or incomplete analgesia, sometimes shorter duration, etc.

For a better outcome in brachial plexus block different drugs like neostigmine, opioids,

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hyaluronidase, and clonidine have been added to local anesthetics so as to obtain quicker onset, good quality, prolonged duration and better postoperative analgesia.[1] Many of these drugs have potential for adverse systemic effects and some of them have questionable efficacy. Midazolam is a water-soluble benzodiazepine. It is used by the epidural or intrathecal route to produce antinociception and to accentuate the effect of local anesthetic. Midazolam acts on Gamma Amino Butyric Acid-A (GABA-A) receptors to give the above effects.[2] These receptors are present in the peripheral nerves also.[3]

In the present study we have attempted to compare the effect of Midazolam-Bupivacaine combination and plain Bupivacaine for brachial plexus block by using the supraclavicular route.

Materials and Methods

This was a prospective randomized single-blind study done in the department of Anesthesia at Osmania General Hospital and Osmania Medical College, Hyderabad. The study included 100 patients posted for upper limb surgeries under supraclavicular block. The patient's age ranged from 15 to 55 years. Informed written consent was obtained from all the patients and in case of minors, consent was taken from the parents. The results were noted in a pre-designed pro forma.

Inclusion criteria

- ASA CLASS I and II
- Patient age between 15 and 55 years, both males and females.
- Systolic blood pressure of 100–139 mm Hg.
- Diastolic blood pressure of 60–89 mm Hg.

Exclusion criteria

- Patients who refused to participate in the study.
- Known cases having hypersensitivity to Midazolam or Bupivacaine.
- Presence of medical complications like severe hypovolemia, septicemia, shock.
- Laboratory tests showing abnormal coagulation profile.
- Presence of local infection.

The following investigations were done in all the patients: Hemoglobin (Hb %), Total Leucocyte Count (TLC), Differential Leucocyte Count (DLC), Bleeding Time (BT), Clotting Time (CT), Random blood sugar (RBS), Blood urea and Serum Creatinine, ECG, HIV, HBs Ag.

Intravenous access with a 20-gauge intravenous (IV) cannula on the contralateral upper limb under aseptic techniques was secured.

The anesthesia machine, emergency oxygen source (E type cylinders) pipeline O_2 supply, working laryngoscopes, appropriate size endotracheal tubes with connectors and oropharyngeal airways, Working suction apparatus with suction catheter were checked.

A multiparameter monitor with pulse oximeter, ECG and Non-invasive blood pressure were used.

Procedure

The patients were randomly divided into two groups of 50 patients each.

Control group–Group-B was given 30 ml Bupivacaine (0.375%). And the Study group–Group BM was given 30 ml of mixture of Bupivacaine (0.375%) and Midazolam (0.05 mg/kg). For the brachial plexus block, a 22G, 5 cm needle, attached to a 20 ml syringe, was passed through the same point, parallel to the head and neck, in a caudal, slightly medial and posterior direction, until either paresthesia was elicited or first rib was encountered.

Anesthesia and analgesia were monitored in all the patients for a period of 24 hours post-surgery. To check the sensory block, temperature testing was done by using cotton soaked in spirit on skin dermatomes C_4 to T_2. To check the motor block, the patient was asked to adduct the shoulder and flex the forearm against gravity.

Onset of sensory block was taken as the time between injection of drug and complete loss of cold perception of the hand, and onset of motor blockade was taken as the time between the injection of drug to inability to adduct arm and flex forearm against gravity, i.e., the patient was unable to touch his/her nose.

Sedation was assessed by a score as described by Culebras *et al.*[4]

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 oxygen saturation were monitored. Duration of sensory block and duration of motor block were also recorded. Intramuscular (IM) injection of Diclofenac sodium was given as rescue analgesia to those who complained of pain. The number of rescue analgesics used within 24 hours after surgery were also noted.

Student's '*t*' test was used to analyze quantitative data and chi-square test was used to analyze qualitative data. A *p* value of < 0.05 was considered statistically significant.

Results

A total of 100 patients were studied with patient's age ranging from 15 to 55 years.

Table 1: Age Distribution of Study Groups

Study groups	Mean ± SD (Age in years)	p value	Significance
Bupivacaine	34.3 ± 11.89	0.375	Not Sig
Bupivacaine + Midazolam	32.3 ± 10.51		

The mean age in Group BM was 32.3 ± 10.5 and in Group B was 34.3 ± 11.8 years. There was no statistically significant difference between the groups (Table 1).

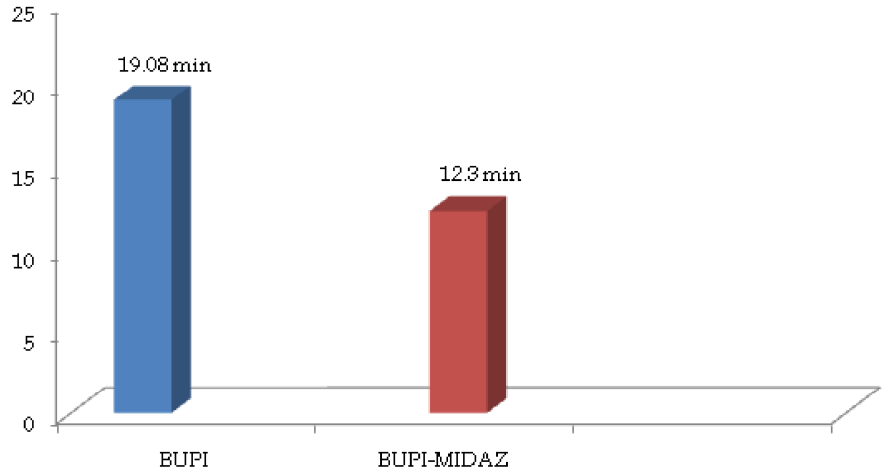

Fig. 1: Time for onset of sensory block (min)

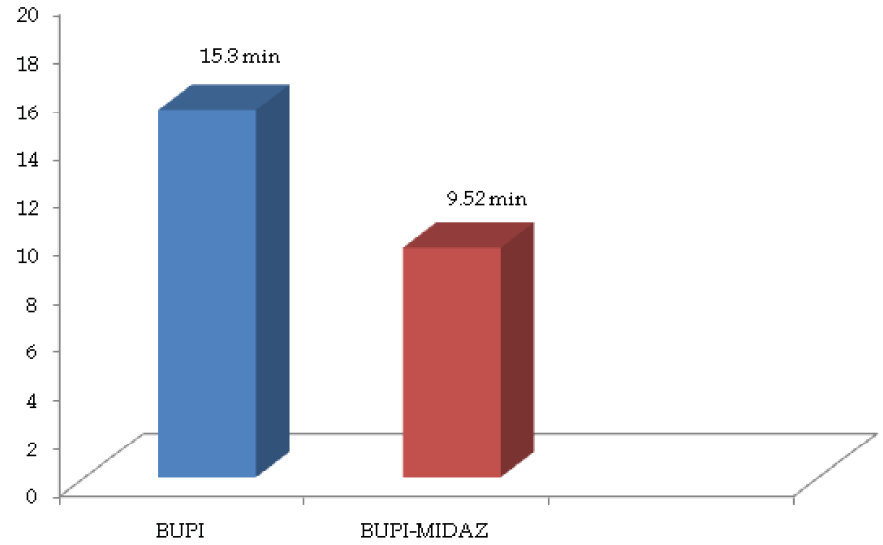

Fig. 2: Time for onset of motor block (min)

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 unpaired student's '*t*' test showed that Group BM had a significantly quicker time for onset of sensory block as compared to Group B ($p < 0.05$) (Fig. 1).

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 unpaired student's '*t*' test showed that that Group BM had a significantly quicker time for onset of motor block as compared to Group B ($p < 0.05$) (Fig. 2).

All the patients were under observation for 24 hours. Time was noted when the patient complained of pain and asked for rescue analgesics. The mean duration of sensory block in group BM and in group B was 13.65 ± 2.01 hours and 6.87 ± 0.89 hours respectively. Group BM had a significantly longer sensory block as compared to Group B ($p < 0.05$) (Fig. 3).

The mean duration of motor block in Group BM and in Group B was 7.23 ± 1.01 hours and 6.17 ± 0.77 hours respectively. Group BM had a statistically significant longer motor block as compared to Group B ($p < 0.05$) (Fig. 4).

Table 2: Number of Rescue Analgesics in Post-op 24 hours

No. of RA 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	

Group BM required less number of rescue analgesics as compared to Group B and it was statistically highly significant (Table 2).

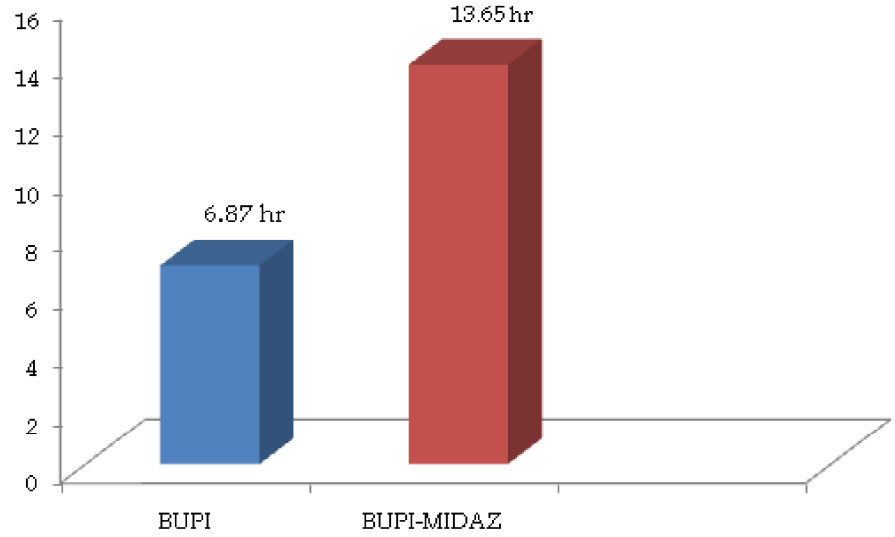

Fig. 3: Duration of sensory block

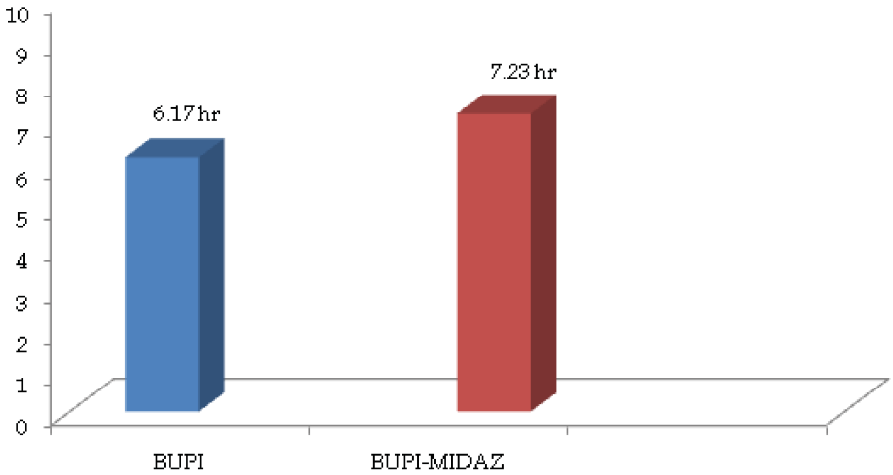

Fig. 4: Duration of motor block

Table 3: Sedation Score in Present Study

Time of Assessment	Scores *	Bupivacaine	Bupivacaine -Midazolam	X^2 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)	$X^2 = 16.74$
	2	0	16 (32)	$p<0.05$ Sig
60 min	1	50 (100)	37 (74)	$X^2 = 12.73$
	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

Sedation score*

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

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. 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 ($p < 0.05$) (Table 3).

Hemodynamic Variables

Pulse rate, systolic BP, diastolic BP, O_2 saturation were recorded at 0 min, 5 min, 15 min, 30 min, 60 min, 2 hours, 6 hours, 12 hours, 24 hours.

Table 4: Pulse Rate (beats/min)

Time of Assessment	Mean+/- SD Bupivacaine	Bupivacaine -Midazolam	*p* value	Significance
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

In Group B, the mean pulse rate ranged from 76 ± 6.2 to 77 ± 6.8 beats/min and in Group BM, it was 74 ± 6.1 to 76 ± 6.7 beats/min. The student's unpaired '*t*' test showed no statistically significant difference between the two groups ($p > 0.05$) (Table 4).

Table 5: Systolic Blood Pressure (mm Hg)

Systolic blood pressure	Mean+/- SD		p value	Significance
Time of Assessment	Bupivacaine (in mm Hg)	Bupivacaine-Midazolam		
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				
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

In Group B, the mean DBP ranged from 75 ± 6.6 to 77 ± 7.4 mm Hg and in Group BM, it was 75 ± 7.11 to 76 ± 7.59 mm Hg. The unpaired student's '*t*' test showed no significant difference between the groups ($p > 0.05$) (Table 5).

Table 6: Oxygen Saturation (%)

Time of Assessment	Mean+/- SD Bupivacaine	Bupivacaine-Midazolam	*p* Value	Significance
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

In Group B, the mean O_2 saturation ranged from 99.7 ± 0.57% to 99.8 ± 0.51% and in Group BM it was from 98 ± 0.5%. The students unpaired '*t*' test showed no significant difference in O_2 saturation

between the two groups ($p > 0.05$) (Table 6).

Discussion

Brachial plexus block confers postoperative analgesia of short duration, even when a long-acting local anesthetic like Bupivacaine is used alone. Different adjuvant drugs like opioids, clonidine, neostigmine and hyaluronidase have been used along with local anesthetics to lengthen the period of analgesia. Many of these drugs were not efficacious or gave rise to adverse effects.

A total of 100 patients with almost an equal male to female ratio were studied. The youngest patient was 15 years and the oldest patient was 55 years. Out of which the mean age of Group B (receiving only Bupivacaine) was 34.3 ± 11.8 years and the mean age of Group BM (receiving Midazolam with Bupivacaine) was 32.3 ± 10.5 years. There was no significant difference between the groups regarding patient age.

In our study we found that the group that received a combination of Midazolam and Bupivacaine showed more rapid onset of sensory and motor blocks that was statistically significantly. Onset of sensory block (Group BM, 12.3 ± 1.5 min; group B, 19.08 ± 1.7 min). Onset of motor block (Group BM, 9.52 ± 1.37 min; Group B, 15.30 ± 2.09 min). This could be attributed to the local anesthetic property of Midazolam that exerts synergistic action when used with local anesthetics. Both the groups had faster onset of motor block than the onset of sensory block. Winnie *et al*.[5] also in their study observed similar findings and attributed it to the fact that in a nerve bundle at the level of the trunks, the motor fibers are located more peripherally than sensory fibers. Hence, when a local anesthetic is injected perineurally, it will block motor fibers first and later blocks the more centrally located sensory fibers.

In the present study, we observed that sensory block lasts longer than motor block and similar finding was noted by de Jong *et al*.[6] It is thought that larger fibers naturally require a higher concentration of local anesthetic than smaller fibers. Large motor fibres require a higher minimal effective concentration of local anesthetic than smaller sensory fibres. Thus, motor function returns 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 hours; Group B, 6.17 ± 0.77 hours). In our study, the mean duration of sensory block was significantly higher ($p < 0.05$) in Group BM than in Group B. (Group BM, 13.65 ± 2.01 hours; Group B, 6.87± 0.89 hours).

A similar study was conducted by Jarbo *et al*.[7] (n = 40) where they observed the efficacy of Midazolam as an adjuvant to Bupivacaine in brachial plexus block. 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 hours; group B, 5.95 ± 1.4 hours) was also longer in group BM than in group B. The duration of motor block was similar between the groups (group BM, 5.65 ± 3.32 hours, group B, 5.1 ± 1.14 hours). 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*.[8] observed better and prolonged postoperative analgesia with Bupivacaine-Midazolam combination as compared to a Bupivacaine-Morphine combination that was given caudally. Nishiyama *et al*.[9] reported better analgesia after adding Midazolam to a continuous epidural infusion of Bupivacaine. Jarbo *et al*.[7] used the intrathecal route for Bupivacaine with Midazolam and observed a significantly lower visual analogue score compared to use of Bupivacaine alone. Midazolam gives this enhanced effect on local anesthetics as it acts on the GABA-A receptor complexes present in the spinal cord. The addition of Midazolam in doses of 1 to 2 mg intrathecally has a positive effect on post-surgical pain and in chronic pain therapy. Intrathecally administered midazolam does not have any neurotoxic effects as demonstrated by animal studies.[9,10] More recently, Tucker and associates demonstrated that administration of 2 mg of intrathecal Midazolam accentuated the analgesic effect of intrathecal Fentanyl in patients in labor. This administration was not associated with any occurrence of neurologic or urologic symptoms.[11]

In our study, the group BM showed lesser requirement of rescue analgesia and lesser mean number of supplemental analgesic boluses. Jarbo *et al*.[7] also reported similar observations. The Group BM also had prolonged analgesia which is attributable to the action of Midazolam on GABA-A receptors of brachial plexus producing antinociception. These receptors are present in peripheral nerves as well. Brown and Marsh

have shown the presence of GABA receptors in peripheral nerve trunks in mammals.[12] Bhisitkul *et al.*[13] have demonstrated the presence of these receptors on both normal and regenerated sensory fibers in peripheral nerves in rats. These receptors are present within the temporomandibular joint and when activated, lead to reduced transmission of nociceptive signals.[14] The action of Midazolam on GABA receptors is well known.

We used Midazolam at a dose of 0.05 mg/kg, for central neuraxial block as it is safe at this dosage and does not cause 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. This is in concurrence with the observations of Jarbo *et al.*[4] 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. Midazolam is highly lipophilic and diffuses quickly into the blood vessels. It has a rapid clearance (6–11 $mL.kg^{-1}.min^{-1}$) and short half-life (1.7–2.6 hours) which contribute to the limited sedation. Though Group BM had higher mean sedation score than Group B ($p < 0.05$) this higher sedation was not significant clinically. In our study, none of the patients experienced airway compromise or required airway assistance. This mild sedation in fact was favorable during that period.

Conclusion

The addition of Midazolam (0.05 mg/kg) as adjuvant to Bupivacaine (0.375%) in brachial plexus block, gives more rapid onset and longer duration of both sensory and motor blocks. It reduces the requirement of rescue analgesics in postoperative period. It provides comfortable sedation intraoperatively without any need for airway assistance and also does not alter the hemodynamic variables. Thus the above combination provides improved analgesia with a prolonged effect.

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