A comparison between 0.375% bupivacaine and 0.375% bupivacaine with midazolam in supraclavicular approach to brachial plexus block for upper limb surgeries

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Abstract

Introduction: 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 epidural or Intrathecal.

Aim: The purpose of this study was to assess the effect of Midazolam added to brachial plexus block by supraclavicular approach.

Materials and Methods: A prospective, randomized, double blinded study was conducted on 100 ASA 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) were administered 30mL of 0.375% Bupivacaine and Group BM (n = 50) were given 30mL of 0.375% Bupivacaine with Midazolam 0.05 mg/kg. The onset time and duration of sensory and motor blockade were recorded. Hemodynamic variables (i.e., heart rate, non-invasive blood pressure, oxygen saturation), sedation scores and rescue analgesic requirements were recorded for 24 hr postoperatively.

Results: The onset of sensory and motor block was significantly faster 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 groups in the post-operative period.

Conclusion: Midazolam (0.05mg/kg) in combination with 30mL 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: Supraclavicular brachial plexus block; Midazolam; Bupivacaine.

Introduction

Peripheral nerve blocks (PNBs) have experienced a remarkable comeback in use, with a broad use in pain management and improved post-operative recovery protocols. While opioids remain the primary analgesics used to relieve pain during surgery, regional anesthetic has improved postoperative discomfort, reduced the use of opioids, and reduced the risk of complications.[1] For both elective and emergency upper limb surgical procedures (plastic, reconstructive, and orthopedic), brachial plexus block (BPB) provides minimally invasive muscle relaxation, sympathetic block, intraoperative hemodynamic stability, and increased postoperative analgesia.[2]

An experienced anesthetist can carry out the surgery safely and with minimal risk of complications, all the while avoiding the systemic side effects of general anesthesia. Although there are other routes, such as interscalene, infraclavicular, and axillary, to successfully execute brachial plexus block, the supraclavicular approach is the most commonly used one.[3] Many adjuvants have been combined with local anesthetics (LAs) to improve the block outcome. Adjuvants such dexamethasone, bicarbonate, clonidine, hyaluronidase, neostigmine, and midazolam have been utilized in clinical settings with LAs to improve postoperative analgesia and enhance peripheral nerve block. Adjuvants reduce the overall dose of LAs, minimizing their harmful effects.[4]

Midazolam, a fast- and short-acting benzodiazepine with an imidazole structure possesses sedative, hypnotic, muscle relaxant, anticonvulsant, anxiolytic, and amnesic effects. Midazolam comes in a variety of formulations to suit various medical requirements. Midazolam is used as an intravenous injection before or during therapeutic, endoscopic, or diagnostic procedures. It also acts as an amnesic, sedative, and anxiolytic. Additionally, it can be

used as a continuous intravenous infusion for sedation in critically ill patients who are intubated and on mechanical ventilation, as part of a balanced anesthetic approach, or for palliative sedation therapy.[5] Gamma-aminobutyric acid (GABA) neurotransmitter activity in the central nervous system is increased by midazolam. It attaches itself to the GABA-A receptor complex's benzodiazepine binding site, which is connected to a chloride ion channel. As a result of this interaction, chloride channels open more frequently, which causes membrane hyperpolarization and inhibits neurons. The pharmacological effects of midazolam result on GABA activity results in pharmacological effects which include sedation, anxiolysis, anterograde amnesia, and muscle relaxation. [5,6] It can also be used to reduce the incidence of postoperative nausea and vomiting (PONV) which can help in improving the anesthesia procedure among patients.[7]

The evidence on the use of midazolam as an adjuvant during BPB is scarce and warrants research. Toward that end, the present study was undertaken as a randomized double blinded trial to evaluate the onset time and analgesic efficacy of Midazolam- Bupivacaine combination compared to plain Bupivacaine (0.375%) with regard to BPB by supraclavicular approach. The aim of the present study was to compare the effectiveness of adding midazolam (0.05mg/kg) to bupivacaine (0.375%) in supraclavicular approach to BPB used for upper limb surgeries versus plain bupivacaine (0.375%).

Material and Methods

The present study randomized double blind trial conducted among patients undergoing upper limb surgeries with a supraclavicular approach to branchial plexus block in a tertiary healthcare center located in Shri Sathya Sai Medical College and Research Institute, Puducherry. The study was conducted after obtaining clearance from the Institutional Human Ethics Committee (IHEC) and were registered as a clinical trial on the Clinical Trial Registry of India (CTRI). Informed consent was obtained by all participants that participated in the present study.

Patients were included in the study if they were aged between 15 to 55 years, belonged to ASA class I or II, had an SBP between 100-139 mm of Hg as well as a DBP of 60-89 mm of Hg. Patients with hypersensitive reaction to Midazolam or other opioids, patients with medical complications like severe anemia, severe hypovolemia, shock, septicemia. abnormal BT, CT or on anticoagulant therapy as well as local infection at the site of proposed puncture for supraclavicular block were excluded from the study.

Procedure

After applying the inclusion and exclusion criteria, 100 patients were involved in the present study and were assigned into 2 groups with 50 patients each. Group A received 30 ml Bupivacaine (0.375%) and Group B received 30 ml of mixture of Bupivacaine (0.375%) and Midazolam (0.05 mg/kg). Patient allocation was done by computer generated randomization table and sealed cover method. The study drug was prepared and administered to the patients by a fellow-anesthetist who did not participate in the study later. After aseptic preparation of area, at a point 1.5 to 2.0cm posterior and cephalad to mid-point of clavicle, subclavian artery pulsation was felt. A skin wheel was raised with local anesthetic just cephalo-posterior to the pulsations. Next, a 22-gauge, 5 cm insulated needle, attached to nerve stimulator, was passed through the same point, parallel to the head and neck, in a caudad, slightly medial and posterior direction, until flexion contraction of fingers was elicited. If the first rib was encountered, the needle was moved over the first rib until flexion contractions of fingers was elicited. After eliciting flexion contraction of fingers and negative aspiration of blood, the study medication was injected. All patients were then monitored for anesthesia and analgesia up to 24 hours post-operatively. Sensory block was evaluated by temperature testing using spirit-soaked cotton on skin dermatomes C4 to T2 whereas motor block was assessed by asking the patient to adduct the shoulder and flex the forearm against gravity. Sedation score described by Culebras et al [8] was used to assess sedation.

Heart rate, non-invasive blood pressure and O2 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) were also recorded. Intramuscular (IM) injection of diclofenac sodium was given as rescue analgesic when patient complained of pain. Number of rescue analgesics in 24 hours of post-operative period was also recorded.

Statistical Analysis

Data was analyzed using SPSS software version 24.0. Categorical variables are presented in a frequency table, and continuous variables are presented in mean ± SD form. Quantitative data was analyzed by student's t-test and qualitative data was analyzed using Chi-square test. A p-value < 0.05 was considered statistically significant.

Results

Hundred patients belonging to ASAI 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 results from table 1 showed that the mean age between the two groups was comparable. With regard to time for onset of sensory and motor block, the difference in mean duration was found to be statistically significant (p<0.001). The difference in duration of sensory block was found to also found statistically significant (p<0.001) while the duration of motor block was found to be comparable (p>0.05).

Figure 1 showed the number of rescue analgesics in post-op 24 hours and the results showed that all the 50 participants in both groups required rescue analgesics and group B had the most participants who only needed 1 analgesic (74%) while most participants in Group A required two analgesics (76%) and 24% participants in group A needed 3 analgesics while none of the participants in group B needed 3 analgesics.

Table 2 showed that in group A, all patients were awake and alert and had sedation score of 1 up to 5 mins. In group B, sedation corresponding to score 2 was observed in some patients between 15 min from time of injection up to 60 min with 20% of patients at 15 min, 32% of patients at 30 min and 26% of patients at 60 min had a sedation score of 2; statistical analysis by chi-square test showed that these difference in sedation score were significant (p<0.05). None of the patients had sedation score of 3 and above during the study period.

In group A, the mean pulse rate ranged from 76±6.0 to 77±7.0 beats/min. In group B, the mean pulse rate ranged from 78±7.0 to 79±7.0 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) (Table 3). In group A, the mean systolic blood pressure ranged from 117±9.85 to 118±10.38 mm of Hg. In group B, the mean systolic blood pressure ranged from 117±10.53 to 118±11.19 mm of Hg. The statistical analysis by unpaired student's t-test showed that there was no significant difference in systolic blood pressure between the two groups (p>0.05) (Table 4). In group A, the mean diastolic blood pressure ranged from 76±6.9 to 77±7.1 mm of Hg. In group B, the mean diastolic blood pressure ranged from 77±6.6 to 77±6.9 mm of Hg. The statistical analysis by student's unpaired t-test showed that there was no significant difference in diastolic blood pressure between the two groups (p>0.05) (Table 5). In group A, the mean O_2 saturation ranged from 98±0.5% to 99±0.57%. In group B, the mean O_2 saturation ranged from 98±0.5%. The statistical analysis by student's unpaired t-test showed that there was no significant difference in O2 saturation between the two groups (p>0.05) (Table 6).

Table 1: Distribution of age, duration of onset of motor and sensory block, duration of motor and sensory block.

Variable	Study group	Mean±SD	Mean difference	t* value	p-value
Age	Group A	33.4±10.81	0.5	0.216	0.83
	Group B	32.9±12.32			
Time for onset of sensory block (min)	Group A	19.08±1.7	7.82	24.13	**<0.001***
	Group B	11.26±1.5			
Time for onset of motor block (min)	Group A	15.30±2.09	5.74	16.38	**<0.001***
	Group B	9.56±1.32			
Duration of sensory block (hours)	Group A	5.84±0.49	7.96	42.2	**<0.001***
	Group B	13.81±1.23			
Duration of motor block (hours)	Group A	5.13±0.45	0.12	1.32	>0.05
	Group B	5.25±0.45			

Table 2: Distribution of sedation scores

Time of assessment	Scores	Bupivacaine	Bupivacaine + Midazolam	X^2 Value, Significance
0 min	1	50 (100)	50 (100)	No significant difference
	2	0	0	
5 mins	1	50 (100)	50 (100)	No significant difference
	2	0	0	
15 mins	1	50 (100)	40 (80)	**X^2 = 9.0, p<0.05* significant difference**
	2	0	10 (20)	
30 mins	1	50 (100)	34 (68)	**X^2 = 16.74, p<0.05* significant difference**
	2	0	16 (32)	
60 mins	1	50 (100)	37 (74)	**X^2 = 12.73, p<0.05* significant difference**
	2	0	13 (26)	
2 hours	1	50 (100)	50 (100)	No significant difference

	2	0	0	
6 hours	**1**	50 (100)	50 (100)	No significant difference
	2	0	0	
12 hours	**1**	50 (100)	50 (100)	No significant difference
	2	0	0	
24 hours	**1**	50 (100)	50 (100)	No significant difference
	2	0	0	

Table 3: Distribution of pulse rate (beats/min) between the two groups

Time of assessment	Mean±SD		Mean difference	t* value	p-value
	Bupivacaine	**Bupivacaine + Midazolam**			
0 min	77±6.8	78±7.4	1.48	1.03	p>0.05
5 mins	77±6.6	78±7.0	1.24	0.91	p>0.05
15 mins	76±7.0	78±7.0	1.44	1.03	p>0.05
30 mins	76±6.6	78±7.4	1.46	1.04	p>0.05
60 mins	77±6.5	78±7.2	1.36	0.99	p>0.05
2 hours	77±7.0	78±7.0	1.1	0.79	p>0.05
6 hours	77±6.6	78±7.0	1.48	1.05	p>0.05
12 hours	76±6	78±7.0	2.04	1.49	p>0.05
24 hours	77±7.0	79±7.0	1.52	1.09	p>0.05

Table 4: Distribution of Systolic blood pressure (mm of Hg) between the two groups

Time of assessment	Mean±SD		Mean difference	t* value	p-value
	Bupivacaine	**Bupivacaine + Midazolam**			
0 min	117 ± 10.45	117 ± 10.53	0.76	0.36	p>0.05
5 mins	118 ± 10.37	117 ± 10.88	0.1	0.047	p>0.05
15 mins	118 ± 010.01	118 ± 10.84	0.08	0.038	p>0.05
30 mins	118 ± 10.38	118 ± 11.01	0.12	0.056	p>0.05
60 mins	118 ± 9.47	117 ± 10.86	0.02	0.01	p>0.05
2 hours	117 ± 10.04	118 ± 10.99	0.7	0.33	p>0.05
6 hours	117 ± 10.01	118 ± 11.19	0.48	0.22	p>0.05
12 hours	117 ± 9.96	118 ± 11.10	0.68	0.32	p>0.05
24 hours	117 ± 9.85	118 ± 11.07	1.04	0.49	p>0.05

Table 5: Distribution of Diastolic blood pressure (mm of Hg) between the two groups

Time of assessment	Mean±SD		Mean difference	t* value	p-value
	Bupivacaine	**Bupivacaine + Midazolam**			
0 min	76 ± 7.72	77 ± 6.8	0.38	0.26	p>0.05
5 mins	76 ±7.52	77 ± 6.74	1.02	0.71	p>0.05
15 mins	76 ± 7.07	77 ± 6.72	1.14	0.82	p>0.05
30 mins	77 ± 7.10	77 ± 6.85	0.38	0.27	p>0.05
60 mins	76 ± 7.03	77 ± 6.66	0.74	0.54	p>0.05
2 hours	76 ± 7.06	77 ± 6.82	0.48	0.34	p>0.05
6 hours	76 ± 7.15	77 ± 6.73	0.52	0.37	p>0.05
12 hours	76 ± 6.9	77 ± 6.92	0.52	0.37	p>0.05
24 hours	76 ± 6.9	77 ± 6.67	0.5	0.36	p>0.05

Table 6: Distribution of oxygen saturation (%) between the two groups

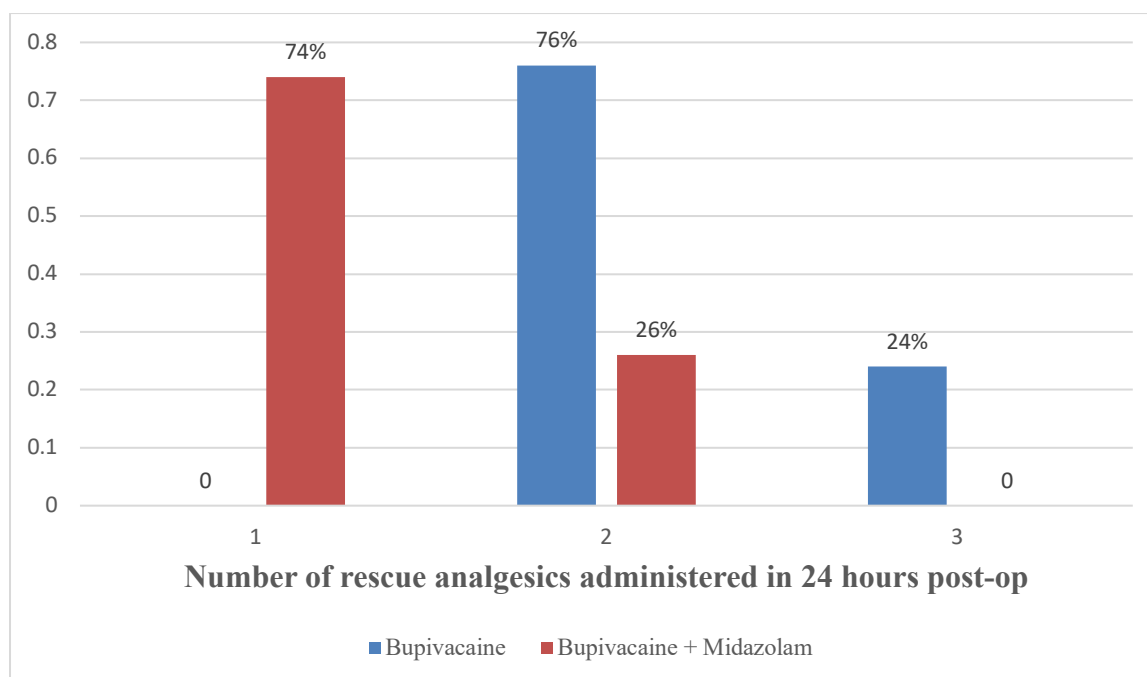| Time of assessment	Mean±SD		t* value	p-value
	Bupivacaine	**Bupivacaine + Midazolam**		
0 min	99 ± 0.56	99 ± 0.49	0	p>0.05
5 mins	99 ± 0.47	98 ± 0.50	1.8	p>0.05
15 mins	99 ± 0.49	99 ± 0.50	0.39	p>0.05
30 mins	98 ± 0.54	98 ± 0.50	2.09	p>0.05
60 mins	99 ± 0.50	98 ± 0.50	0.19	p>0.05
2 hours	99 ± 0.48	99 ± 0.47	0.2	p>0.05
6 hours	99 ± 0.49	99 ± 0.47	2.45	p>0.05
12 hours	99 ± 0.57	99 ± 0.46	2.09	p>0.05
24 hours	99 ± 0.48	99 ± 0.46	3.58	p>0.05

Figure 1: Number of rescue analgesics in post-op 24 hours

Discussion

Supraclavicular brachial plexus block (BPB) is an excellent substitute for general anesthesia during upper limb operations. It prevents the undesirable effects of using general anesthesia and upper airway instruments. Moreover, it reduces the duration of hospitalization and costs and provides complete muscle relaxation. [9,10] The addition of adjuncts help by enhancing the effect of anesthetic used along with minimizing the side effects. One such adjuvant used is midazolam which has been found to be effective as an additional adjuvant in cessarian and lower abdominal surgeries. [11,12]

The present study assessed a hundred patients belonging to ASAI and II posted for upper limb surgeries under supraclavicular brachial plexus block. The mean age between the participants involved in the present study was 33 years and comparable among the two groups. This was close to the results from a study conducted by Shaikh SI et al wherein the mean age of the participant's undergoing BPB was 34.40 years. [9] It can be inferred that this age group is more prone to suffer from accidents that can result in upper limb injuries requiring surgery compared to other age groups.

The mean duration for onset of sensory and motor block was found to be significantly different between the two groups (p<0.001) with midazolam group showing a lower duration of onset, this difference was also observed with regard to the duration of sensory block, but midazolam group reported the higher duration of sedation. However, the mean difference in the duration of motor block between the two groups was not significant (p>0.05). This contrasted the results from a

previous study wherein the different in mean duration of onset with respect to sensory and motor block among patients who receive and do not receive midazolam during BPB was not significant (p>0.05) while the difference in mean duration of motor block between the groups was significant (p<0.001). [9] Patients who were administered midazolam as an adjunct were found to experience longer sensory and motor blocks when compared to another adjunct (neostigmine) in a study conducted by Sayyed HG et al. [10] Multiple other studies have revealed faster onset of sensory and motor block associated with midazolam as an adjunct to BPB. [13-18] However, studies by Kantharaja HE et al and El-Baradey GF et al reported that dexamethasone was superior to midazolam as an adjunct with a faster sensory and motor block along with longer duration of sensory and motor blockades. [19,20] This result can be explained by the action of midazolam on GABA neurotransmitter activity resulting in membrane hyperpolarization and inhibition of neurons bringing about faster onset of sedation and increased duration of anesthetic activity and sedation.

The number of rescue analgesics were administered to all participants within 24 hours post-op but group B requiring a considerably lower number of analgesics compared to group A. This result was in alignment with that of a previously conducted studies where the mean duration of pain relief was significantly lower among the group of patients who were administered midazolam as an adjunct to BPB. [9,13-18] Prolonged analgesia was also observed while administering BPB with midazolam as an adjunct compared to neostigmine which is

associated with lower requirement for analgesics. [10] However, it was found to inferior to clonidine as an adjunct with regard to duration of post operative analgesia in a study by Patil B et al. [21] When used with other opioid drugs, midazolam can augment their analgesic effects. Better analgesia may result from the benzodiazepine-induced drowsiness and anxiolysis in addition to the opioids' pain-relieving effects.

All of the patients in the two groups were awake and alert with a sedation score of 1 at 5 minutes. Between the time of sedation to 15 minutes up to 60 minutes, sedation corresponding to score 2 was observed in 20% of patients at 15 min, 32% of patients at 30 min and 26% of patients at 60 min. None of the patients had sedation score of 3 and above during the study period. After this, all the participants in both groups reported a score of one from 2 hours up to 24 hours. A significantly higher sedation score was seen in the group with was administered midazolam as an adjunct to BPB among patients in a previously conducted studies which was similar to the results of the present study. [9,18] Another previously conducted study showed that the midazolam adjunct group reported a sedation score of 2 between 15 mins from the time of sedation to 60 mins similar to the present study.[13] A previously conducted study reported that midazolam was superior to dexamethasone with regard to sedation scores when used an adjunct in supraclavicular BPB.[20] Midazolam is a strong sedative that acts quickly and mainly via increasing GABA activity in the central nervous system. Interactions with other drugs might increase or lessen its sedative effects, and adverse responses require constant monitoring to avoid.

With regard to hemodynamic variables, the difference in mean pulse rate, systolic blood pressure, diastolic blood pressure and oxygen saturation was not found to be statistically significant at all times of assessment from time of sedation to 24 hours (p>0.05). These results resonated with that of a previously conducted study wherein heart rate, mean blood pressure and oxygen saturation was found to be comparable between groups using midazolam, dexamethasone and epinephrine as adjuncts during supraclavicular BBP.[20] A previously conducted study reported that the group which was administered midazolam as an adjunct reported a significantly higher respiratory rate from 10 to 30 minutes after sedation (p<0.001) which was not observed in the present study.[9] These findings can be attributed to the anxiolytic action of midazolam by potentiating the effects of GABA in the central nervous system, leading to a calming effect. Its muscle relaxant properties can complement the effects of other anesthetic drugs leading to controlled hemodynamic conditions.

The drawbacks of the present study involve the lack of comparison of the adjunctive effects of midazolam with other alternatives such as dexamethasone, clonidine, bicarbonate, hyaluronidase, neostigmine, among others. The advantages of the study include the extensive assessments that have been conducted with regard to the duration of sensory and motor sedation onset, duration of sedation, emergency analgesia and duration of post operative analgesia. The clinical implications of the results obtained in the present study are that midazolam is an effective adjuvant that can be used along with supraclavicular route of BPB to ensure a safe and complication free anesthetic procedure. Its advantages over other adjuvants should be studied further so that clinicians and surgeons can make an informed decision on the type of adjuvant to be used to provide the best care to patients.

Conclusion

The results of the present study help conclude that midazolam is an effective adjunct that can be used in BPB that is administered via supraclavicular route. It can help in reducing the duration of onset of sedation, increase the duration of sedation and analgesic effects which can help in patient management post operatively helping in pain management and recovery of the patient.

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