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Research Article

Efficacy of midazolam co-administered along with local anaesthetic solution in brachial plexus block

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Abstract

Objectives: To compare the onset, duration, postoperative pain scores, time of first rescue analgesic required in supraclavicular block with local anaesthetic solution along with –midazolam 50 µg /kg.

Methods: A randomized double blind study was carried out on 70 patients of ASA grade I and II undergoing upper limb orthopedic surgeries, were divided in two groups. Group A(n=35) received Inj. Bupivacaine (0.5%) 20 ml + Inj. Lignocaine with adrenaline (1:200000) 10ml .Group B(n=35) received Inj. Bupivacaine 0.5% (20 ml) + Inj. Lignocaine with adrenaline (1:200000) 10 ml + Inj. Midazolam 50 µg/kg as an adjuvant in supraclavicular brachial plexus block .The duration of sensory block, motor block, duration of post operative analgesia, sedation score and visual analogue score were obtained in both groups and values were compared with 'unpaired t-test'.

Result: The onset and duration of sensory and motor block was significantly faster and longer in group B compared to group A ($p < 0.05$). Pain scores were significantly lower in group B for 24 hours postoperatively ($p < 0.001$). Demand for rescue analgesic were significantly less in group B. ($p<0.05$).

Conclusion: the addition of midazolam to local anaesthetics in supraclavicular block prolongs onset and duration of blockade, enhances post op analgesia with stable hemodynamic and desirable sedation score without any adverse effects.

Keywords: Supraclavicular brachial block, Midazolam, Bupivacaine

1. Introduction

A supraclavicular approach for blockade of the brachial plexus was first described by Kulenkampff[1] in 1911. Brachial plexus blocks are very useful alternative to general anaesthesia for upper limb surgery. With the brachial plexus block we can achieve ideal operating conditions by producing complete muscular relaxation, maintaining stable intraoperative hemodynamic and the associated sympathetic block. The sympathetic block decreases oedema, postoperative pain and vasospasm .There are various studies which investigated several adjuncts, including opioids[2], clonidine[3], dexamethasone[4], neostigmine[5], hyaluronidase[6] and bicarbonate.

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 aminobutyric acid-A (GABA-A) receptors.[7] Very little data is available on the effect of adding midazolam to a local anaesthetic solution in brachial plexus block. So present study was carried out to determine the duration of sensory and motor blockade and to determine analgesic efficacy of midazolam added to local anaesthetic solution in supraclavicular brachial plexus block.

2. Methods

After approval from the Institutional Ethics Committee a controlled prospective clinical study was carried out at P.D.U Medical College, Rajkot, Gujarat in the year may 2011-2012. Informed written consent was taken from the patients. The study was carried out in 70 patients of ASA grade I and II, aged 12-69 years scheduled for elective and emergency upper limb orthopedic surgeries under supraclavicular brachial plexus block. Patients with known hypersensitivity to local anaesthetic drugs, bleeding disorders, uncontrolled diabetes mellitus, renal and liver diseases, circulatory instability, pregnant women, patients with epilepsy and peptic disease were excluded from study.

All the patients were subjected to detailed preanaesthetic evaluation. Routine investigations and specific investigations were done as per patient clinical evaluation. All patients were taught about pain scale regarding VAS scale preoperatively. Haemodynamic variables (HR, BP, O2 saturation) should also have been evaluated.

Patients were randomly divided into two groups of 35 patients each. Randomization done with computer generated numbers, they put in white envelops. After selection of envelope by patient, the odd number was considered as group A cases and even number considered group B cases. Anesthesiologist performing the block was blinded to the drug solution used.

Group A Inj. Bupivacaine (0.5%) 20 ml+ Inj. Lignocaine (2%) 10 ml with Inj. Adrenaline (1: 2,00,000)

Group B Inj. Bupivacaine (0.5%) 20 ml+ Inj. Lignocaine (2%) 10 ml with Inj. Adrenaline (1: 2,00,000) + Inj. Midazolam 50 µg/kg (preservative free).

2.1 Anaesthetic technique

All patients were kept nil by mouth for at least 6 hours .An intravenous line was secured. Pulse oxymeter, non invasive blood pressure cuff and ECG electrodes were applied and baseline pulse rate, blood pressure, respiratory rate, sedation scores and pain score were recorded.

All patients were premedicated with Inj. Glycopyrrolate 0.2 mg intravenously, Inj. Ondansetron 4 mg intravenously and Inj. Ranitidine 50 mg intravenously. All patients were sedated with Inj.Midazolam 1 mg i.v. The patient was made to lie in supine position with both the arms adducted and straight a roller pack was kept between two scapula. Head was turned away from the side to be blocked. Under all aseptic and antiseptic precautions the pulsation of subclavian artery was palpated with thumb of one hand at 1cm above the mid- point of clavicle and the point of maximum pulsation was marked. While placing the thumb on the pulsation of subclavian artery it is displaced medially, the needle was introduced just lateral to artery 1cm above clavicle. A 22-gauge short bevel 60-mm insulated needle was used connected to a nerve locator, which was set to deliver impulses of 1 mA (frequency 1

Hz, 50–500 ms). The needle was considered to be placed correctly when contraction of either the biceps or muscle groups in the forearm was seen. Once the jerk is elicited the current was gradually reduced to 0.6 mA; after aspiration to exclude intravascular placement, the local anaesthetic mixture was injected. 35ml of drug mixture was given after careful negative aspiration (Aspiration for blood before injection to avoid accidental intravenous injection. Coming back of anaesthetic solution from same needle also confirms presence of needle with in sheath). Onset of block was also confirmed by absence of motor response by current. Immediately after drug injection, massage was done for 3 minutes for even distribution of drug.

After completion of procedure oxygen at 3 lit/min was given via nasal prongs.

Assessment of sensory block was done at 0min, 1min, 2min, 3min, 4min, 5min, 6min, and 6.5min till 15 minutes after completion of drug injection in skin areas corresponding to median nerve, radial nerve, ulnar nerve and musculocutaneous nerve.

Grade-0: Anaesthesia - no sensation felt
Grade-1: Analgesia- dull sensation felt
Grade-2: Sharp pain felt

Radial nerve on dorsum of hand at base of index finger, median nerve on Palmer base of index finger, ulnar nerve by Palmer base of little finger and musculocutaneous nerve –on along lateral border of forearm over site of radial artery.

Time to peak sensory effect was considered when there was complete loss of sensation to pin prick along all the above mentioned nerve distribution.

Motor block was determined according to a modified Bromage scale for upper extremities. Assessment was carried out at 0min, 1min, 2min, 3min, 5min, 6min, 8 min,10 min and15min after drug injection. Individual nerves can be tested as follows.

Radial nerve by extension of distal phalanx of thumb, median nerve by thumb opposition, ulnar nerve by thumb adduction and musculocutaneous nerve by flexion of forearm.

Grade – 0: Complete paralysis
Grade – 1: Paresis
Grade – 2: Normal muscle force.

Thus block was considered completely effective when all segments supplied by median, radial, ulnar and musculocutaneous nerve had anaesthesia (Analgesia + Paralysis). Intra-operatively patients were monitored for hemodynamic variables such as Pulse rate, Blood pressure and Respiratory rate. Sedation score is assessed by the Ramsay sedation score (evaluated at every 15 minutes)

2.2 Post Operative Assessment

- Total duration of surgery
- Total duration of sensory blockade (Time interval between injection of drug and complete recovery of sensation)
- Total duration of motor blockade (Time interval between injection of drug and complete recovery of motor power)
- Time of rescue analgesics given when vas pain score >4

Post-operatively pulse, Blood pressure, Respiratory rate, consciousness, sedation and response to verbal commands were noted. Patients were examined for duration of analgesia as per Visual Analogue Scale (VAS). VAS score is the most commonly used methods of assessing acute pain and its relief.

3. Results

3.1 Hemodynamic parameters

Table 1: Hemodynamic variability, Pulse Rate at different intervals

TIME (MIN)	Group A (N=35)	Group B (N=35)	p value*	Significance	Confidence interval
B/F block	84.6±8	84.8±8	0.7	Not significant	-8.2-5.6
0	86±7.7	85.6±8.4	0.71	Not significant	-4.7-3.2
5	84.8±8	85±8.5	0.93	Not significant	-4.1-3.8
10	84.9±3	84.3±8	0.75	Not significant	-3.4-4.1
15	85.2±7.8	84.9±7.8	0.9	Not significant	-3.5-4
30	85.4±7.3	85±7.8	0.8	Not significant	-3.2-4.1
60	85.8±7.5	85.4±7.7	0.8	Not significant	-3.2-4.1
120	85.6±7.9	85.2±7.7	0.84	Not significant	-4.1-3.4

* Students unpaired t test

In group A mean pulse rate ranges from 84.6±8 to 86±7.7 and in group B 84.3±8 to 85.6±8.4. There is no statistically significant difference in pulse rate of the patients between the two groups (p>0.05).

Table 2: Hemodynamic variability SBP at different intervals

TIME (MIN)	Group A (N=35)	Group B (N=35)	p value*	Significance	Confidence interval
B/F block	120.5±8.3	122.2±9.8	0.4	Not significant	-6.1-2.6
0	119±8	121.8±9.4	0.2	Not significant	-6.9-1.5
5	118±8.2	122±9.8	0.1	Not significant	-7.9-0.86
10	118 ±8	122±9.8	0.07	Not significant	-8.2-0.4
15	117.6±8.1	121±9.4	0.05	Not significant	-8.4-0.1
30	117.4±7.6	121±9.2	0.07	Not significant	-7.8-0.3
60	117.9±7.8	121±9.7	0.09	Not significant	-7.8-0.6
120	117.7±7.7	120±9.4	0.1	Not significant	-7.2-1.1

*Students unpaired t test

In group A mean systolic blood pressure ranges from 117.4± to 120.5±8.3 and in group B 120±9.4 to 122.2±9.8. There is no statistically significant difference in systolic blood pressure of the patients between the two groups.(p>0.05)

Table 3: Hemodynamic variability DBP at different intervals

TIME (MIN)	Group A (N=35)	Group B (N=35)	p value*	Significance	Confidence interval
B/F block	76.8±5.2	76.8±5	0.9	Not significant	-2.6-2.5
0	75.1±4.9	76.4±4.9	0.2	Not significant	-3.6-1.1
5	76.9±5.4	76.5±5.6	0.2	Not significant	-4.2-1.1
10	74.9±5	76.5±5.7	0.2	Not significant	-4.2-1
15	74.2±5.5	76.5±5.1	0.1	Not significant	-4.5-06
30	74.6±5.3	76.5±5	0.2	Not significant	-4-0.9
60	75.5±5.1	76±5.4	0.5	Not significant	-3.3-1.7
120	74.8±4.8	76.6±5.4	0.1	Not significant	-4.2-0.7

*Students unpaired t test

In group A mean diastolic blood pressure ranges from 74.2±5.5 to76.9 ±5.4 and in group B 76±5.4 to 76.8±5. There is no statistically significant difference in diastolic blood pressure of the patients between the two groups.(p>0.05)

Table 4: Hemodynamic variability oxygen saturation at different intervals

TIME (MIN)	Group A (N=35)	Group B (N=35)	p value*	Significance	Confidence interval
B/F block	98.5±0.4	98.4±0.5	0.8	Not significant	-0.2-0.2
0	98.5±0.4	98.4±0.5	0.8	Not significant	-0.2-0.2
5	98.5±0.4	98.4±0.5	0.09	Not significant	-0.03-0.4
10	98.4±0.4	98.3±0.5	0.05	Not significant	-0.4-0.06
15	98.4±0.4	98.4±0.4	0.1	Not significant	-0.04-0.4
30	98.6±0.4	98.4±0.5	1	Not significant	-0.2-0.2
60	98.7±0.4	98.4±0.5	0.09	Not significant	-0.03-0.4
120	98.5±0.4	98.4±0.5	0.3	Not significant	-0.1-0.3

*Students unpaired t test

In group A mean oxygen saturation ranges from 98.5±0.4 to98.7 ±0.4 and in group B 98.3±0.5 to 98.4±0.5. There is no statistically significant difference oxygen saturation of the patients between the two groups. (p>0.05)

Table 5: Characteristics of block

	Group A (n=35)	Group B (n=35)	P value*	Significance	Confidence interval
Onset of Sensory block (min)	19.02±1.8	11.6±1.39	<0.0001	significant	6.5 -8.18
Onset of motor block (min)	15.6±1.8	11.15±0.8	<0.0001	Significant	5.1-6.7
Duration of sensory block(hrs)	6.14±0.6	9.6±1.1	<0.0001	significant	5.9-5.02
Duration of motor block (hrs)	4.6±0.69	4.9±0.48	0.4988	Not significant	-0.57-0.003

The onset of sensory and motor block was faster in group B .The mean time for onset of sensory block in group B was 11. 6 ± 1.39 minutes and in group A was 19.02 ± 1.8 min. The mean time for duration of sensory block in group A was 6.14±0.6 minutes and group B 9.6±1.1minutes .

The mean time for onset of motor block in group A was 15.6±1.8 min and in group B was 11.15±0.8 min. The mean time duration of motor block in group A was 4.6±0.69 and in group B 4.9±0.48 .There was no significant difference in duration of motor block in both the groups.(p>0.05)

Table 6: No. of Rescue analgesics given in post op 24 hr

	No. of RA given in post 24 hrs		% of RA given in post 24 hrs	
	Group A (n=35)	Group B (n=35)	Group A (n=35)	Group B (n=35)
1	0	23	0	65.71
2	20	12	57.14	34.28
3	15	0	42.85	0

Chi square test χ^2=49.26, p<0.0001

In group A 57.14% patients required 2 doses of rescue analgesics and 42.85 % required 3 doses of rescue analgesic in post 24 hr while in group B 65.71% patients required 1 dose of rescue analgesic and 34.28% required 2 doses of rescue analgesic post op 24 hr. The number of rescue analgesic required was statistically significant.(p<0.05)

Table 6 Pain Score in post operative 24 hrs

TIME (HRS)	Group A (n=35)	Group B (n=35)	p value*	significance	Confidence interval
1	0	0	0	-	-
4	0	0	0	-	-
6	0	1.6±1.9	<0.0001	Significant	-2.9
8	4.7±0.9	0.14±0.4	<0.0001	Significant	4.08-4.8
12	5.5±0.6	4±1.6	<0.0001	Significant	0.8-2.1
24	6±0.7	4..8±0.5	<0.0001	Significant	0.6-1.6

*Students unpaired t test

Duration of post operative analgesia was significantly longer in group B. In first four hour the pain score was zero in both the groups. Patients in group B had significantly lower pain score at 6 hr, 8 hr, 12 hr, 24 hr.

3.2 Sedation score

In group B 31.4% of patients at 15 min, 65.7% of patients at 30 min and 51.4% of patients at 60 min has sedation score of 2 is sedated, but responding to verbal stimulus. In group A all patients had sedation score of 1 i.e. awake and alert. The sedation in group B patients was mild and desirable, without any need for airway assistance. This difference was statistically significant (P < 0.05).

4. Discussion

Regional anaesthesia techniques are often used to provide not only anaesthesia but also postoperative analgesia after surgery. Brachial plexus block is a versatile and reliable regional anaesthesia technique and suitable alternative to general anaesthesia for upper limb surgery.

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[2], Clonidine[3],Dexamethasone[4], Neostigmine[5] and Hyaluronidase[6] 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.

It a has been studied extensively as an adjuvant to local anaesthetic in subarachnoid block[8,9,10,11,12,13,14] for its antinociceptive action and thereby potentiating the effect of local anaesthetic and prolonging duration or analgesia with no systemic side effects. Midazolam produces this effect by its action on GABA receptors. GABA receptors are also found in peripheral nerves. Benzodiazepine potentiates and prolongs duration of analgesia through its antinociceptive action on GABA receptors and also has desirable properties of stable hemodynamic, sedation, less respiratory depression

Going through the literature, only three studies are[15,16,17] available wherein midazolam was used as an adjuvant to local anaesthetic in peripheral nerve block with the claim that this combination provides earlier onset , longer duration and better quality of analgesia in comparison to local anaesthetic used alone. There is need for future research in this field which prompted us to carry out this clinical study.

Characteristics of block

The onset of sensory and motor block was significantly faster in patients who received combination of local anaesthetics and midazolam. This could be due to a local anaesthetic property of Midazolam and its synergistic action with that of local anaesthetics.

Similar study done by Koj (2005)[15]. They observed faster onset of sensory and motor block in group BM compared to control group ($P<0.05$). The mean onset time for sensory block was 12±2.9minutes in group BM compared to 20±3.8 minutes in control group. The mean onset time for motor block was 9.2±2.38 minutes compared to 17.1±3.83 minutes in control group B.

Gautam and Bhatta[18] also observed faster onset of sensory and motor block in midazolam group II (XBM). Sensory block in group I was12 ±4.2 minutes, in group II 6 ±3.1minutes, motor block in group I was 11±2.3 minutes, group II 5±4.2 minutes.

In our study, the mean duration of sensory block was significantly longer ($P<0.05$) in group B than in group A .Group A was 6.14±0.6 and group minutes B 9.6±1.1 minutes.

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 B . In group A 57.14% patients required 2 doses of rescue analgesics and 42.85 % required 3 doses of rescue analgesic in post 24 hr while in group B 65.71% patients required 1 dose of rescue analgesic and 34.28% required 2 doses of rescue analgesic postoperative 24 hr.

The prolonged analgesia in Group B could be due to the action of Midazolam on GABA-A receptors present in the brachial plexus and thus producing antinociception. Brown and Marsh [19] demonstrated GABA receptors in mammalian peripheral nerve trunk. Bhisitkul *et al*.[20], showed that axonal GABA receptors are present on both normal and regenerated sensory fibres in rat peripheral nerve.

Patients were examined for duration of analgesia as per visual analogue scale (VAS). Significantly lower pain score was observed in group B. Patients in group B had significantly lower pain score at 6 hr,8 hr,12 hr,24 hr.($p<0.005$)

Batra *et al*[14] 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. Nishiyama *et al*[8]., added Midazolam to a continuous epidural infusion of Bupivacaine and observed improved analgesia. The addition of Midazolam in doses of approximately 1 to 2 mg intrathecally has a positive effect on perioperative and chronic pain therapy.

In our study mean sedation score was higher in group B as compared to group A, starting 15 minutes after injecting the drug and lasted until 60 minutes. The highest sedation score was 2.In group B 31.4% patients were sedated at 15 minutes, 65.7% at 30 minutes and 51.4% patients at 60 minutes were sedated with sedation score of 2. This mild sedation was actually desirable during that period. No patient experienced airway compromise or required airway assistance.

Similar results were observed by Desai (2013)[21]. They found that 73.33% patients were having sedation score of 2 in group A (midazolam) while in control group all patients were found to be alert i.e. sedation score 0. Both the results were comparable to our study.

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).

In our study SpO_2 remain fairly stable and comparable in both the group. This shows striking safety of midazolam with sedation as none of the patient required any airway assistance.

4. Complications

We did not observed any complications in our study related to the drugs used or the technique of the block .No post operative complications like nausea, vomiting , convulsions , bradycardia , hypotension, chest pain were observed during the study period.

5. Conclusion

We concluded that the addition of Midazolam 50mcg/kg as an adjuvant, fasten onset of sensory block and motor block, prolongs duration of sensory block. It also improves postoperative analgesia, reduces requirement of rescue analgesics in postoperative periods and provides desirable sedation without any side effects.

References

1. Kulenkampf D. Anesthesia of the brachial plexus. Zentralbl *Chir*. 1911; 38:1337-50.
2. Bazin JE, Massoni C, Bruelle P, Fenies V, Groslier D, Schoeffler P. The addition of local anaesthetics in brachial plexus block: The comparative effects of morphine, buprenorphine and sufentanil. *Anaesthesia*. 1997; 52:858-62.
3. Culebras X, Van Gessel E, Hoffmeyer P, Gamulin Z. Clonidine combined with a long acting local anaesthetic does not prolong postoperative analgesia after brachial plexus block but does induce hemodynamic changes. *Anesth Analg*. 2001; 92:199–204.
4. Shrestha BR, Maharjan SK, Shrestha S, Gautam B, Thapa C, Thapa PB *et al*. Comparative study between tramadol and dexamethasone as an admixture to bupivacaine in supraclavicular brachial plexus block. *J Nepal Med Assoc*. 2007; 46(168):158-64.
5. Bone HG, van Aken H, Brooke M, Burkle H, Brooke M, Burkle H. Enhancement of axillary brachial plexus block anaesthesia by coadministration of neostigmine. *Reg Anesth Pain Med*. 1999; 24:405-10.
6. Keeler JF, Simpson KH, Ellis FR, Kay SP. Effect of addition of hyaluronidase to bupivacaine during axillary brachial plexus block. *Br J Anaesth*. 1992;68:68-71
7. Edwards M, Serrao JM, Winnie AP, Tay CH, Patel KP, Ramamurthy S, Durrani Z. Pharmacokinetics of local anaesthetics during plexus blocks. *Anesth Analg* 1977; 56: 852–61.

8. Nishiyama T, Yokoyama T, Hanaoka K. Midazolam improves postoperative epidural analgesia with continuous infusion of local anaesthetics. *Can J Anaesth* 1998; 45:551–5.
9. Goodchild CS, Guo Z, Musgreave A, Gent JP. Antinociception by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid receptors. *Br J Anaesth* 1996; 77:758-63.
10. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. *Br J Anaesth* 2001;86 :77-9
11. Palsule VS, Shibu Leena. Prolongation of analgesia by addition of midazolam to intrathecal Bupivacaine. *Indian J pain*. 2008; 22:148-151.
12. Agrawal N, A. Usmani, R Shegal, Rakesh Kumar, Bhadoria P. Effect of intrathecal midazolam bupivaine on postoperative analgesia. *Indian J Anaesth*. 2005; 49(1):37-39.
13. Kohno T, Kumamoto E, Baba H, Atakt T, Okomoto M, Shimoji K, Yoshimura M. Action of midazolam on GABAergic transmission in substantia gelatinosa neurons of adult rat spinal cord slices. *Anaesthesiology*. 2000; 92(2):507-15.
14. Mahajan R, Batra YK, Grover VK, Kajal J. A comparative study of caudal bupivacaine and midazolam-bupivacaine mixture for post-operative analgesia in children undergoing genitourinary surgery. *Int J Clin Pharmacol Ther* 2001; 39(3):116-20.
15. Koj J, Yatindra KB, Nidhi BP. Brachial plexus block with midazolam and bupivacaine improves analgesia. *Can J Anesth* 2005; 52:822-6.
16. Laiq N, Mohammad Naeem Khan, Arif M and Shahid Khan Midazolam with Bupivacaine for Improving Analgesia Quality in Brachial Plexus Block for Upper Limb. *Surgeries Journal of the College of Physicians and Surgeons Pakistan* 2008; 18 (11): 674-678.
17. Min Soo Kim, Bum Sang Hwang, Byeong Mun Hwang, Seong Sik Kang, Hee Jeong Son, Young cheong, and Hye Jean lee, The effect of the Addition of Fentanyl and midazolam to lidocaine in supraclavicular brachial plexus block. *Korean J anaesthesiology*. 2008; 54(2):167-172.
18. SN Gautam, SN Bhatta. A comparision on brachial plexua block using local anaesthetic agent with and without midazolam. *Journal of Chitwan Medical College* 2013; 3(3): 11-13.
19. Brown DA, Marsh S. Axonal GABA-receptors in mammalian peripheral nerve trunks. *Brain Res* 1978; 156:187–91.
20. Bhisitkul RB, Villa JE, Kocsis JD. Axonal GABA receptors are selectively present on normal and regenerated sensory fibers in rat peripheral nerves. *Exp Brain Res* 1987; 66: 659–63.
21. Desai D, Garg M effect of addition of Midazolam as an adjuvant to local anaesthetics in supraclavicular brachial plexus block, I.M.A.G.S.B. *News Bulletine* 2013; 8:49-53.