A comparative study of 0.375% bupivacaine with midazolam and 0.375% bupivacaine for brachial plexus block in upper limb surgeries

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ABSTRACT

Background: Brachial plexus block is useful as a sole regional anesthesia technique or as an adjunct to general anaesthesia for providing ideal operating conditions in upper limb surgeries. Adjuvants to local anesthetics for brachial plexus block may enhance the quality and duration of analgesia. Midazolam, a water-soluble benzodiazepine, is known to enhance the effect of local anesthetics.
Methods: A prospective, randomized, single blinded study was conducted on 100 ASA Grade I or II adult patients undergoing elective upper limb surgeries under single injection supraclavicular brachial plexus block. Patients were randomly divided into two groups. Group I (n = 50) - 30mL of 0.375% Bupivacaine and Group II (n = 50) - 30mL of 0.375% Bupivacaine and preservative free Midazolam 0.05 mg/kg was used . Onset time and duration of sensory and motor blockade were recorded. Haemodynamic variables (i.e., Heart rate, Blood pressure and Oxygen saturation), Sedation scores and rescue analgesic requirements were recorded for 24 hr postoperatively.
Results: The onset and duration of sensory and motor block was significantly faster in Group II compared to Group I ($p < 0.05$). The duration of sensory and motor block was significantly longer in Group II compared to Group I ($p < 0.05$). Rescue analgesic requirements were significantly less in Group II compared to Group I ($p < 0.05$) . Haemodynamics did not differ between groups in the post-operative period.
Conclusion: Midazolam (0.05mg/kg) when used as an adjuvant to 0.375% Bupivacaine in brachial plexus block potentiated onset of sensory and motor block, and improved postoperative analgesia without any adverse events.

Keywords: Bupivacaine,Midazolam,Supraclavicular brachial plexus block,Postoperative analgesia.

Introduction

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:

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

Bupivacaine 0.5% is an amide local anesthetics has

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been associated with cardiotoxicity when used in high concentration. Single-injection techniques are limited by pharmacological duration and therapeutic index of local anaesthetics (LAs). Patients undergoing upper limb procedures with single-injection supraclavicular blocks are frequently hospitalized overnight due to inadequate pain relief [3] after resolution of blocks. A method of prolonging analgesia without extra cost and logistical difficulties of indwelling catheters would benefit both patients and their care givers. Many drugs have been studied as adjuvants for single-injection regional anaesthetic techniques like Neostigmine, Opioids, Hyaluronidase, and Clonidine etc [1-3] in order to modify the block in terms of quick onset, good quality, prolonged duration and post-operative analgesia. Midazolam a water soluble, short acting benzodiazepine , synthesized by Walsar and colleagues in 1976[1] that was produced primarily for use in anaesthesia[2].Midazolam produces antinociception by acting on GABA-A receptors . Extrasynaptic receptors for GABA are present on myelinated axons of peripheral nerves. Many studies have shown midazolam when used with local anesthetics (LA) through various routes prolongs analgesia. An earlier study was done by Koj Jarbo *et al*[1] has shown the same results .So the present study is being undertaken in a randomized single blinded manner to evaluate onset time and analgesic efficacy of Midazolam 0.05 mg/kg plus 0.375% Bupivacaine combination in comparison to 0.375% Bupivacaine for single injection brachial plexus block by supraclavicular approach.

Materials and methods

This study was carried out between November 2013 and October 2015 in Department of Anaesthesiology at Osmania General Hospital, attached to Osmania Medical College, Hyderabad . After Hospital Ethics committee approval and informed consent from all patients a prospective, randomized, single blinded study was undertaken in 100 patients of age group of 15 to 55 yrs posted for elective upper limb surgeries under single injection supraclavicular block. Results were recorded using a pre-set proforma.

Inclusion criteria

- ASA CLASS I & II
- Aged between 15 to 55 years.
- SBP → 100 – 139mm of Hg.
- DBP → 60 – 89mm of Hg.

Exclusion criteria

- ASA≥ III
- Patient refusal.
- Patients with medical complications like shock, septicaemia etc.,
- Patients on antiplatelets / anticoagulants or with abnormal coagulation profile.
- Local infection at the site of injection.
- History of substance abuse

Pre-operative investigations included Hb%, ECG, RBS, Blood urea, Serum creatinine and Viral screening. In the operating rooms a 20 G i.v. cannula inserted on the contralateral upper limb. Equipment for emergency airway resuscitation was kept ready. A multiparameter monitor (Philips intellivue MP20) was connected and moitored ECG , SpO_2 and NIBP..

Procedure

100 adult patients were enrolled in the study and randomly assigned to 2 groups containing 50 patients in each.

- Group-I - Control group –: received 30 ml Bupivacaine (0.375%)
- Group – II - Study group: received 30 ml Bupivacaine (0.375%) + Midazolam (0.05 mg/kg).

Supraclavicular Brachial plexus block was performed under aseptic precautions, after eliciting paraesthesia respective test drugs were injected perineurally in both groups. 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

HR, NIBP 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) were also recorded. IM injection of Diclofenac sodium was used as rescue analgesic.

Assessment of Sensory Block

1) Onset Of Sensory Block: a) Subjective assessment: Time interval between administrations of local anaesthetic to the time patient first indicates relief of pain. b) Objective assessment: Time interval between administration of local anaesthetic to complete analgesia of forearm in relation to the distribution of each major nerve as tested by pinprick over the forearm between elbow and wrist (areas of open wound excluded).

Grading of sensory blockade

Grade 0 = Normal sensation
Grade 1 = Blunted sensation (analgesia)
Grade 2 = Absence of sensation
2) Duration between times of onset of sensory block to the time when patient first complains of pain at the site of surgery.

Assessment of Pain

Verbal Rating Scale **(VRS)** was used to assess the level of pain perceived by the patient. A VRS consists of a list of adjectives describing different levels of pain severity. Patients are asked to inspect the list of adjectives and select the word or phrase that best describes their level of pain.

Table 1: Score and intensity

Score	Intensity
0	No Pain
1	Mild Pain
2	Moderate Pain
3	Severe Pain
4	Very Severe Pain

Assessment of Motor Block: a) Onset of Motor Block: Time interval between administrations of local anaesthetic to the time when finger movements are lost completely. b) Duration Of Motor Block: Duration between the times of loss of finger movements to the time the patient first regains his finger movements.

Grading Of Motor Blockade

Grade 0 - No blockade
Grade 1- Loss of movements at elbow joint
Grade 2 - Loss of movements at wrist joint
Grade 3 - Loss of finger movements.
Number of rescue analgesics in 24hrs of post operative period would also be recorded.
Results were analysed by 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.

Result

100 ASA physical status I and II patients of either sex aged between 15-55 years, posted for upper limb surgeries under supraclavicular brachial plexus block were selected randomly for the study .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. The mean age of the patients in group BM was 32.3 ± 10.51 and in group B was34.3 ± 11.89 years. Age incidences between two groups were comparable.

Table 1: Time for onset of sensory and motor block (min)

Onset of sensory block	Onset time (min)	p value	Significance
I	19.08 ± 1.7	< 0.001	HS
II	12.3 ± 1.35		
Onset of motor block			
I	15.30 ± 2.09	< 0.001	HS
II	9.52 ± 1.37		

HS- Highly Significant

The mean time for onset of sensory block in group II was 12.3 ± 1.35 min and in group I was 19.08 ± 1.7 min, significantly faster when compared to group I (p< 0.05).

The mean time for onset of motor block in group II was 9.52 ± 1.37 min and in group II was 15.3 ± 2.09 min is significantly faster when compared to group B (p< 0.05).

Table 2: Duration of sensory and motor block

Sensory block	Duration of block (hrs)	p value	Significance
I	6.87 ± 0.89	P < 0.001	HS
II	13.65 ± 2.01		
Motor block			
I	6.17 ± 0.77	p < 0.001	SS
II	7.23 ± 1.01		

HS- statistically highly significant.

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 I was 6.87 ± 0.89 hours. The statistical analysis by students unpaired 't' test showed that the duration of sensory block in group II was significantly longer when compared to group I (p< 0.05).The mean duration of motor block in group II was 7.23 ± 1.01 hours and the group I 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).

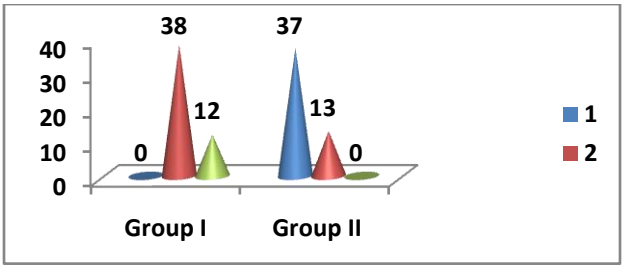

Figure 1: Number of rescue Analgesics needed post operatively

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

In group II, 74% patients required only 1 rescue analgesic dosage and 26% of patients required 2 rescue analgesic doses in post-op 24 hours. In group I 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 ($\chi^2 = 61.25$, $P < 0.0001$)

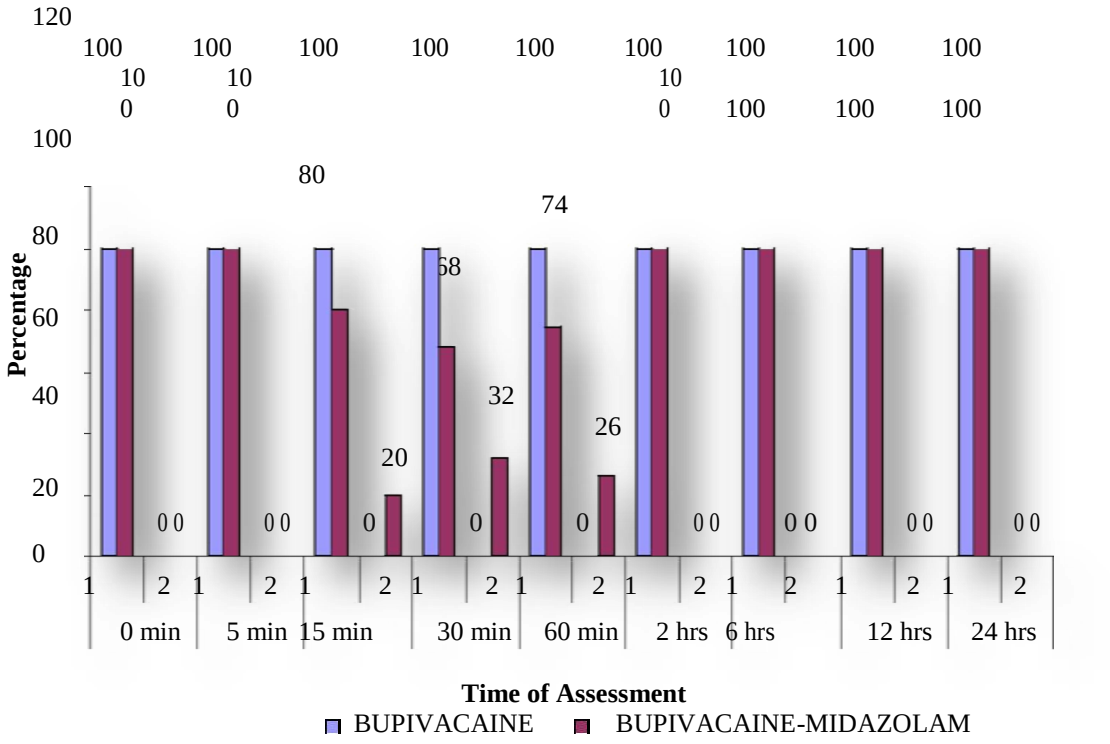

Figure 2: Sedation score

In group I, all patients were awake and alert and had sedation score of 1. In group II, 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 ($P < 0.05$).

In group I, the mean pulse rate ranged from 76 ± 6.2 to 77 ± 6.8 beats / min.

In group II, 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 I, the mean diastolic blood pressure ranged from 75 ± 6.6 to 77 ± 7.4 mm of Hg. In group II, 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 I, the mean O_2 saturation ranged from 99.7 ± 0.57% to 99.8 ± 0.51%. In group II, 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 ($p > 0.05$).

Discussion

Adjuncts to local anesthetics have been added in order to shorten the onset time, increase the quality and

duration of brachial plexus block resulting in smooth postoperative outcome. Various adjuvant drugs like Opioids, Clonidine, Dexamethasone , Neostigmine and Hyaluronidase have been evaluated in conjunction with local anaesthetics to prolong the period of analgesia with limitations due to side effects. Midazolam is known to produce antinociception and enhance the effect of local anaesthetic when administered intrathecally and epidurally. It produces this effect by its action on GABA receptors found in peripheral nerves.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 I (receiving only 0.375% Bupivacaine) was 34.3 ± 11.89 years and the mean age of group II (receiving Midazolam + 0.375% 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 0.375% bupivacaine. Onset of sensory block (group II 12.3 ± 1.5 min; group I, 19.08 ± 1.7 min). Onset of motor block (group II , 9.52 ± 1.37 min;group I, 15.30 ± 2.09 min).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*[4]., 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 tends to last longer as compared to motor block which agrees with the observation by de Jong *et al*[5]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) fibers 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 [5]. In our study duration of motor blocks were different between the groups. (Group II, 7.23 ± 1.01 hrs; group I, 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 II than in group I. (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[1] 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, and 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*[6], found that a Bupivacaine and Midazolam combination prolonged postoperative analgesia compared to a Bupivacaine – Morphine combination when administered caudally. Nishiyama *et al*[7], added Midazolam to a continuous epidural infusion of Bupivacaine and observed improved analgesia. Batra *et al*[1], 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[1].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. Bhisitkul *et al* [13], showed that axonal GABA receptors are present on both normal and regenerated sensory fibres in rat

peripheral nerve. Cairns *et al* [14], 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. 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 II (0.375% Bupivacaine +Midazolam) compared to Group I (0.375%Bupivacaine), 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 [1]. 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 $mL.kg^{-1}.min^{-1}$) 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. No patient experienced airway compromise or required airway assistance. This mild sedation was actually desirable during that period.

Conclusion

In conclusion, Midazolam 0.05 mg/kg when added to 30 ml of0.375% Bupivacaine for single injection percutaneous supraclavicular brachial plexus block, significantly speeds the onset of sensory and motor blocks ($p< 0.05$). The combination produces prolonged superior analgesia , resulting in reduced requirements for rescue analgesics and also has desirable properties of stable hemodynamics, sedation, less respiratory depression.

References

1. Jarbo K, Batra YK, Panda NB. Brachial plexus block with midazolam and bupivacaine improves analgesia. Can J Anaesth 2005;52:822-826.
2. Casati A, Putzu M. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? Best Pract Res Clin Anaesthesiol 2005; 19:247-68.
3. Rawal N, Hylander J, Nydahl PA, Olofsson I, Gupta A. Survey of Postoperative analgesia following ambulatory surgery. Acta Anaesthesiol Scand 1997;41:1017-22.
4. Winnie AP, Tay CH, Patel KP, Ramamurthy S, Durrani Z. Pharmacokinetics of local anaesthetics during plexus blocks. Anesth Analg 1977;56:852-61.
5. De Jong RH, Wagman IH. Physiological mechanism of peripheral nerve block by local anaesthetics. Anesthesiology 1963;24:684-727.
6. Gulec S, Buyukkidan B, Oral N, Ozcan N, Tanriverdi B. Comparison of caudal bupivacaine, bupivacaine-morphine and bupivacaine-midazolam mixtures for post-operative analgesia in children. Eur J Anaesthesiol 1998;15:161-5.
7. Nishiyama T, Matsukawa T, Hanaoka K. Acute phase histopathological study of spinally administered midazolam in cats. Anesth Analg 1999;89:717-20.
8. Serrao JM, Marks RL, Morby SJ, Good child CS. Intrathecal midazolam for the treatment of chronic mechanical low back pain : controlled comparison with epidural steroid in a pilot study. Pain 1992;48:5-12.
9. Serrao JM, Mac Kenzie JM, Good Child CS, Gent JP. Intrathecal midazolam in the rat : an investigation of possible neurotoxic effects. Eur J Pharmacol 1990;7:115-22.
10. Nishiyama T, Matsukawa T, Hanaoka K. Acute phase histopathological study of spinally administered midazolam in cats. Anesth Analg 1999;89:717-20.
11. Schiweiger IM, Jorge-Costa M, Pizzolato GP, Foster A, Morel DR. Intrathecal midazolam reduces isoflurane MAC and increases the apnoeic threshold in rats. Can J Anaesth 1994;41:144-8.
12. Tucker AP, Lai C, Nadeson R, Goodchild CS. Intrathecal midazolam I : A cohort study investigating safety. Anesth Analg 2004;98:1512-20.
13. Bhisitkul RB, Villa JE, Kocsis JD. Axonal GABA receptors are selectively present on normal and regenerated sensory fibres in rat peripheral nerves. Exp Brain Res 1987;66:659-63.
14. Cairns BE, Sessle BJ, Hu JW. Activation of peripheral GABA – A receptors inhibits temporo-mandibular joint-evoked jaw muscle activity. J Neurophysiology 1999;81:1966-9.

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