INTRODUCTION

A supraclavicular approach for blockade of the brachial plexus was first described by Kulenkampf in 1911.1 It is the most commonly used approach in providing surgical anaesthesia. In recent years, the technique has gained importance as regional anaesthetic technique for surgical, diagnostic and therapeutic purposes in interventional pain management. It includes blocking of the brachial plexus where it is most compactly arranged, with less requirement of the anaesthetic solution and rapid onset of action.2 It provides ideal conditions for surgery, maintains stable hemodynamics intraoperatively, decreases vasospasm, edema and postoperative pain. Because of bupivacaine's long duration of action, it is used most frequently among local anaesthetics for brachial plexus block.3

Several adjuvants have been studied so far, including opioids, clonidine, neostigmine, hyaluronidase, bicarbonate, and dexamethasone.4 Addition of any of the above agents to brachial plexus block is supposed to prolong the analgesic effect without any unwanted systemic effects and should also reduce the total requirement of local anaesthetic used. Midazolam is known to produce antinociception and potentiate the effect of local anaesthetic when given in neuraxial block. It produces this effect by its action on Gamma-Aminobutyric Acid-A (GABA-A) receptors and peripheral nerves contain these receptors.5,6 Very little data is available on the effect of adding midazolam to a local anaesthetic solution in peripheral nerve blocks.

The objective of this study was to determine the onset time, duration and postoperative pain scores of supraclavicular block with bupivacaine alone and bupivacaine-midazolam combination.

METHODOLOGY

A randomized controlled clinical trial was conducted at the Postgraduate Medical Institute, Hayatabad Medical Complex, Peshawar, from April 2005 to June 2007. Patients in group A were administered 30 ml of 0.5% bupivacaine and those in group B were given 30 ml of 0.5% bupivacaine with midazolam 50 µg·kg⁻¹. Hemodynamic variables (heart rate, noninvasive blood pressure, oxygen saturation), pain scores, rescue analgesic requirements and sedation score were recorded for 24 hours postoperatively, and compared using ANOVA with significance at p < 0.05.

Results: The onset and duration of sensory and motor block was significantly faster and longer in group B compared to group A (p < 0.001). 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. Hemodynamics and sedation scores did not differ between the groups in the studied period.

Conclusion: Bupivacaine (0.5%) in combination with Midazolam (50 µg·kg⁻¹) quickened the onset as well as prolonged the duration of sensory and motor blockade of the brachial plexus for upper limb surgery. It improved postoperative analgesia without producing any adverse events compared to plain bupivacaine (0.5%) in equal volume.

Key words: Supraclavicular block. Midazolam. Brachial plexus block. Bupivacaine.
envelopes, 25 for each group, were made and a randomly-selected envelope was opened when the patient presented. The inclusion criteria were ASA-I or II adult patients presenting for surgery on the elbow, forearm, wrist or hand. Patients having pregnancy, diabetes, recent drug intake (within 24 hours), previous nerve injury, and uncooperative patients were excluded. Standard venous cannulation and ASA monitors were applied. Every patient was lightly sedated with midazolam 1 mg intravenously. A senior and experienced anaesthesiologist performed the brachial plexus block, using a supraclavicular approach. Each patient was placed in supine position, with the head turned to opposite side and the ipsilateral arm adducted. The interscalene groove and pulsation of the subclavian artery above the mid point of the clavicle posterior to clavicular head of the sternocleidomastoid were identified. After aseptic preparation of the area at a point, 1-2 cm above and posterior to arterial pulsation, a skin wheal was raised with local anaesthetic. A 22-G, 4 cm needle was passed through the same point in a backward, inward and downward direction until paresthesia was elicited in the hand or arm. After eliciting paresthesia and negative aspiration for blood, the study medication was injected.

Patients in group A received 30 ml of 0.5% bupivacaaine while those in group B received 30 ml of bupivacaaine 0.5% along with preservative-free midazolam 50 µg·kg⁻¹. After injection, patients were assessed for sensory blockade by using pinprick. The palmar surfaces of the index and little finger were used to test the median and ulnar nerve in the hand respectively. The dorsal surface of the thumb was used to test the radial nerve. The end of the injection was considered time 0. The sensory tests were conducted at 5, 10, 15, and 20 minutes and every 5 minutes thereafter, if necessary, upto 30 minutes. The sensory blockade was considered to be successful if it occurred within < 30 minutes, whereas motor block was assessed by asking the patient to adduct the shoulder and flex the fore-arm and hand against gravity.

Time to analgesia was defined as the time taken from the end of the injection to the first dull response to pinprick in the distribution of any of the three sensory nerves in the hand. Time to anesthesia was defined as the time between injection and the complete development of anaesthesia (no sensation reported to pinprick) in all three sensory sites. Patients having complete motor block were included in the study. Duration of sensory block (the time taken between injection of the drug and appearance of pain requiring analgesia) and duration of motor block (time taken between injection to complete return of motor power) were recorded.

Sedation score was assessed by using the sedation scale described by Culebras et al.⁴ (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). Heart rate, noninvasive blood pressure, oxygen saturation and sedation score were measured every 5 minutes until the end of surgery. Pain was assessed using the Visual Analogue Scale (VAS) where zero (0) represented no pain, and 10 meant the worst possible pain. Injection tramadol 1 mg·kg⁻¹ i.v. was given as rescue analgesic when the pain score was more than 4. Postoperatively heart rate, noninvasive blood pressure, pain and sedation scores were recorded at 0 minutes, 30 minutes, 1st hour, 6th hour, 12th hour and 24th hour (Figure 1).

The patients were shifted to recovery room after the procedure and followed for 24 hours either in the ward or contacted by phone. Specific questions were asked about any residual numbness, discomfort and pain. The patients were also asked to evaluate their experience as satisfactory, neutral or unsatisfactory.

Sample size was calculated as expected success rate in group B (bupivacaine-midazolam) and group A (bupivacaine) being 85% and 45% respectively, ratio in two groups being 1:1 for precision of 5% and study power at 80%. The sample size for each group was 25. All results were expressed as mean ± SD (standard deviation). Statistical analysis were performed using SPSS version 10. Unpaired t-test was used to compare age, weight, duration of surgery, intraoperative hemodynamic variables (heart rate, systolic and diastolic blood pressure and oxygen saturation). Onset and duration of sensory and motor block, pain scores (VAS), sedation scores and the requirement for rescue analgesia were also compared in two groups using analysis of variance (ANOVA). A p-value less than 0.05 was considered statistically significant.

**RESULTS**

A total of 50 patients fulfilled the inclusion criteria. They were randomly divided into two groups of 25 each.
No significant difference were found among the two groups with respect to mean age, gender distribution, weight, duration of surgery and ASA physical status (Table I).

Onset of sensory and motor block appeared earlier in group B than in group A (p < 0.001). In group B, the onset of sensory block occurred in 14 ± 3.1 minutes compared to 22 ± 3.5 minutes in group A. Onset time of motor block in group B was 10.5 ± 2.40 minutes compared to 18.5 ± 3.50 minutes in group A (Table II). The mean duration of complete analgesia was significantly prolonged (p=0.002) in the bupivacaine-midazolam group (Table II).

Lower pain scores were observed in group B compared to group A for 24 hours postoperatively (p < 0.001, Table III). Almost all patients in group A required rescue analgesia, while only 5 patients (20%) of group B required rescue analgesics (p <0.001) in order to maintain analgesia in the first 24 hours.

**Table I:** Demographic characteristics (mean ± SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=25)</th>
<th>Group B (n=25)</th>
<th>Significance p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>32.5±2.47</td>
<td>33.1±1.46</td>
<td>0.3010</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.2±7.87</td>
<td>60.4±8.87</td>
<td>0.6159</td>
</tr>
<tr>
<td>Duration of surgery (minutes)</td>
<td>42.8±3.88</td>
<td>44.6±5.39</td>
<td>0.1817</td>
</tr>
<tr>
<td>M/F</td>
<td>15/10</td>
<td>13/12</td>
<td></td>
</tr>
<tr>
<td>ASA physical status (II/III)</td>
<td>20/5</td>
<td>18/7</td>
<td></td>
</tr>
</tbody>
</table>

**Table II:** Characteristics of sensory and motor blocks in two groups.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group A (n=25)</th>
<th>Group B (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset (minutes)</td>
<td>22±3.5</td>
<td>14±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration (hours)</td>
<td>6.20±1.8</td>
<td>9.30±4.50</td>
<td>0.0025</td>
</tr>
<tr>
<td>Motor block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset (minutes)</td>
<td>18.5±3.5</td>
<td>10.5±2.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration (hours)</td>
<td>5.20±2.10</td>
<td>7.65±3.20</td>
<td>0.0024</td>
</tr>
</tbody>
</table>

**Table III:** Postoperative pain score in two groups.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group A (n=25)</th>
<th>Group B (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>VAS (mean±SD)</td>
<td>VAS (mean±SD)</td>
<td></td>
</tr>
<tr>
<td>(n=25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6th</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(hour)</td>
<td>2±1.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>12th</td>
<td>2±0.3</td>
<td>2±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(hour)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24th</td>
<td>3±0.4</td>
<td>3±0.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Perioperatively sedation scores were higher in group B compared to group A (p < 0.001) as patients in group A were all awake (score 1) throughout the intraoperative period while in group B, 6 patients at 10 minutes, 10 patients at 20 minutes and 15 patients at 30 minutes were sedated and responded to verbal stimulation (score 2). The highest sedation score was 2 in group B and no patient had sedation score of 3 or more that required assistance for airway maintenance. Sedation scores did not differ between groups in the postoperative period.

Haemodynamic variables i.e. heart rate, systolic blood pressure, diastolic blood pressure and oxygen saturation were comparable between groups and did not change significantly in the intraoperative or postoperative period. No adverse event was encountered in either group of patients.

**DISCUSSION**

Among the local anaesthetics used for brachial plexus block, bupivacaine is used most frequently because of its long duration of action. In spite of that, brachial plexus block provides postoperative analgesia of short duration when used alone. Various additive agents have been tried in combination with local anaesthetics to prolong the period of analgesia. Majority were found to be either ineffective or producing unacceptable adverse effects. Limited research has been done on the effect of adding midazolam to the analgesic characteristics produced by local anaesthetics in peripheral nerve blocks. In this study, the onset of sensory and motor blocks, duration of anaesthesia and analgesia and quality of block was found to be significantly faster and prolonged in patients who received a combination of midazolam and bupivacaine. This could be due to a local antinociceptive effect of midazolam and its additive and synergistic action with that of local anaesthetics.

For the last few years non-opioids like ketamine, clonidine and midazolam have been tried as adjuvants in regional techniques to prolong postoperative analgesia as well as surgical time for intraoperative procedures in single shot regional techniques.

Several studies showed midazolam to be effective when used in intrathecal, epidural and caudal blocks and now recently midazolam with bupivacaine has been found to improve analgesic characteristics in peripheral blocks compared to bupivacaine alone. Mahajan et al. observed clinically and statistically prolonged postoperative analgesic effects in bupivacaine-midazolam group compared to plain bupivacaine in caudal block. Gulec et al. also noticed bupivacaine-midazolam to provide prolonged postoperative analgesia compared to bupivacaine-morphine combination when given caudally. A significantly lower visual analogue score was observed by Batra et al. when bupivacaine was used in combination with midazolam intrathecally compared to bupivacaine alone. Due to the high blood concentration of benzodiazepine through conventional routes and profound sedation, proper assessment of analgesic effect was difficult to obtain. With the advent of the less toxic water soluble benzodiazepine (midazolam), it became possible to use it directly over the nerve tissues. Midazolam produces this additive effect on local anaesthetics by its action on the GABA-A receptor complexes present in the spinal cord. Animal studies have revealed no damage to the spinal cord, nerve roots or meninges.
Midazolam in doses of 1-2 mg in spinal block has a positive effect on perioperative and chronic pain therapy.14 Parkash and Joshi used two different concentrations of midazolam and demonstrated prolonged analgesia without any unwanted effects with higher concentrations.15 No evidence of neurologic or urologic symptoms have been observed by administration of 2 mg intrathecal midazolam.16 In this study, midazolam was used at a dose of 50 µg·kg⁻¹ without any significant adverse effects, as in other studies, the same dosage was used in central neuraxial block.11,12

More recently, Tucker and associates observed enhance analgesic effects by administration of intrathecal midazolam in combination with intrathecal fentanyl in labouring patients.17 Batra and Tomoki also obtained effective analgesia with intrathecal midazolam without observing any adverse effects.18 The mechanism by which midazolam causes prolonged analgesia could be due to its action on GABA-A receptors present in the brachial plexus and thus producing antinociception. The action of midazolam on GABA receptors is well-established. Various researchers have demonstrated the presence of GABA receptors in peripheral nerves. The presence of GABA receptors within the temporomandibular joint were observed by Cairns et al. and that its activation could decrease the transmission of nociceptive signals.6 In vitro autoradiography of lamina-II of the dorsal horn in the human spinal cord has shown the presence of high density of benzodiazepine (GABA-A) receptors suggesting a possible role in pain modulation.19

Goodchild and Serrao reported the analgesic effects of benzodiazepines at the spinal cord level in animals.20 Analgesic efficacy of intrathecal midazolam in humans has been demonstrated recently. The opioid antagonist naltrindole acts on δ-receptors and suppresses the antinociceptive effect of intrathecal midazolam, suggesting that intrathecal midazolam is responsible for the release of an endogenous opioid acting at spinal δ-receptors.21

Sedation scores were higher in patients in group B compared to group A in this study, at 20 minutes after injecting the agent until 30 minutes postoperatively. This could be due to systemic absorption of the drug (midazolam) and its effect on central nervous system to produce sedation.22 Though mean sedation score in group B was higher as compared to group A, there was no clinically significant sedation in patients in group B. The highest sedation score was 2, i.e. the patient was asleep and responding to verbal stimulus. No patient experienced airway compromise or required airway assistance.

In this study, blood pressure, heart rate, respiratory rate and oxygen saturation remained stable throughout the procedure and postoperatively as they did not differ significantly during the study period.

Pneumothorax is a possible complication when attempting supraclavicular block. The published incidence of pneumothorax varies between 1% and 4% using the classical supraclavicular approach and paresthesia for nerve localization.23 To minimize the incidence of pneumothorax, several alternative supraclavicular approaches have been described.24 The subclavian perivascular approach has been shown to have less incidence of pneumothorax.25 To minimize the risk of pneumothorax, the subclavian perivascular approach was used in this study and no clinically significant pneumothorax occurred in either studied group.

CONCLUSION

Combination of midazolam 50 µg·kg⁻¹ to 30 ml of 0.5% of bupivacaine for supraclavicular brachial plexus block quickened the onset of sensory and motor blocks. It also improved quality of analgesia as manifested by lower pain scores, a prolonged effect and reduced requirements for rescue analgesics.

REFERENCES

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