Effect of Nimodipine as an Adjunct to Lidocaine for Brachial Plexus Blocks

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Abstracts

There is growing evidence that nimodipine, an L-type dihydropyridine calcium channel blocker with relatively high blood-brain barrier penetration, enhances the sensory block and duration of analgesia of local anesthetic. The aim of this study was to evaluate whether additional anesthetic and analgesic effects could be derived from co-administration of nimodipine with lignocaine injected into brachial plexus sheath.

Forty patients undergoing upper limb surgery aged between 25-45 years of both sex were randomized by closed envelope to receive either lidocaine infusion alone (group A) or lidocaine infusion preceded by nimodipine infusion at the dose of 10 ml/h (group B) in a double-blind study design. There was significant decrease in mean arterial pressure and increase in the heart rate in the group B in comparison to group A most of times from preoperative to 6 hours postoperative.

A marginal decrease in the onset time of sensory block was noticed in group B as compared to group A, which was statistically not significant (p>0.05). Significant prolongation of the duration of sensory block was observed in group B as compared to group A (p<0.05). There was non-significant difference in the duration of analgesia or motor block in the two groups (p > 0.05).

At the 6th hour postoperatively, the sensory block score at first request to analgesia was marginally decreased in early postoperative in group B as compared to group A, which was statistically not significant in all postoperative period.

Our study suggested that co-administration of nimodipine with lignocaine injection into brachial plexus sheath caused significant prolongation of the duration of sensory blockade with minor effect on cardiovascular system.

Introduction:

Regional anesthesia can provide a combination of minimal systemic impairment and excellent localized postoperative analgesia. Regional anesthesia minimizes costs because conduct of the anesthetic itself generates little cost, and operating room time can be reduced by placing the block preoperatively, whereas recovery from the anesthetic facilitates early ambulatory patient discharge (Gerancher, 2000). The first brachial plexus block was performed in 1885 with cocaine by Halstead. In 1911, Hirschell described the first percutaneous technique for performing the block (Buttner, 1998). Opioids are the mainstay of treating acute postoperative pain. However, they are associated with a number of adverse events, including nausea, vomiting, respiratory depression, mood alteration, and pruritus. Treatment with adjunctive analgesic drugs can have a morphine-sparing effect, thereby reducing these side effects. This has been demonstrated with nonsteroidal anti-inflammatory drugs, such as diclofenac, but these drugs are associated with adverse events profile, including gastrointestinal hemorrhage and renal impairment (Ng et al, 2002). In recent years it has gained popularity with addition of various adjuncts to local anesthetic solution in an attempt to increase its efficacy and duration. Systemic adverse effects and prolonged motor block are avoided along with a reduction in total dose of local anesthetic used. Adjuncts like epinephrine, bicarbonate, opioids, clonidine, neostigmine and tramadol have been injected concomitantly with local anesthetic solution (Culebras, et al, 2001).

There is growing evidence suggesting that calcium is involved in endogenous regulation of pain sensitivity and substances with calcium channel blocking effect have antinociceptive properties (Fassoulaki, et al, 1997). Voltage-gated calcium channels have an important role in the transmission of noxious impulses. Calcium influx and eflux from sensory neurons appears to facilitate nociceptive neurotransmitter release in the spinal cord (Ben Sreti et al, 1983). Increases in intracellular calcium are associated with development of central sensitization after a noxious insult (Coderre et al, 1993). So inhibition of calcium into sensory neurons using calcium antagonists might reduce pain and requirement for morphine in clinical situations (Omore et al, 1995). Nimodipine is a dihydropyridine calcium channel antagonist, which binds to the L-type voltage gated calcium channel. It crosses the blood-brain barrier and is demonstrably effective in the prevention of secondary ischemic neurological damage after subarachnoid hemorrhage (Allen et al, 1983). The primary action of local anesthetics reversibly blocks conduction of the nerve impulses by preventing increases in the permeability of the nerve membrane to the sodium ions. Calcium movement is essential for the normal sensory processing and plays a role in axonal conduction and synaptic transmission. It had been reported that local anesthetics depress influx of calcium ions at concentration required to block nerve conduction (palade, 1985). Local anesthetics such as lignocaine, procaine, amylcaine or cinchocaine have been shown to inhibit calcium uptake and the calcium ion-activated ATPase activity of sarcoplasmic reticulum vesicles. This ability of local anesthetic agents to inhibit calcium efflux from the sarcoplasmic reticulum was explained by incorporation of these amphiphilic drugs into the
lipid layer, interaction with calcium ion binding sites on membrane phospholipids, or direct interaction with a calcium channel (Iwasaki et al., 1996).

**Patients and methods:**
This prospective clinically randomized study was carried out on forty adult patients, aged 25–45 years, ASA physical status I & II, scheduled for elective upper limb (forearm and hand) orthopedic surgery at Mansoura University Hospitals. The protocol of the study was approved by the responsible authorities and after obtaining Hospital Ethics Committee approval and written informed patient consent, the anesthetic procedure was explained to the patients. Exclusion criteria were weight below 60 or above 100 kg; patient refusal; infection at the site of injection; patients receiving anticoagulants or calcium channel blockers; history of peripheral neuropathies; cardiac conduction abnormalities; coagulation disorders; hypersensitivity to local anesthetic agents; major liver or kidney disease. Other exclusion criteria were uncontrolled hypertension (because of the potential vasoactive properties of nimodipine), patients on concurrent medication for coronary artery disease, congestive cardiac failure, and known allergy to calcium antagonists. The trial medication was withheld and the patient was withdrawn from the study, if the patient had a systolic blood pressure less than 100 mm Hg at the time the drug was due for administration. Preoperative sedation was achieved 30 min before surgery with IV midazolam 5 mg. The patients were randomly allocated into two groups of 20 patients each by closed envelopes technique. After placement of routine monitors which includes; pulse oximetry, ECG, and non-invasive arterial blood pressure, all patients were administered brachial plexus block by supra-claviculur approach, where the patients lie in the supine position with the head rotated to other side. Detect the interscalene groove and the clavicle. The needle entry site is posterior to the midpoint of the clavicle. Prepare the skin for aseptic technique and infiltrate with a local anesthetic. 5 cm 22-gauge needle is inserted in a caudal direction, and advanced downwards, backwards and medially until parasthesia is felt (Brown, 1992). Local anesthetic solution was injected only after obtaining parasthesia at the dose of 3 mg/kg of lidocaine and 1 mg/kg of bupivacaine. This is done in the form of 50 ml of 1% lidocaine with 0.25% bupivacaine solution and this procedure was guided by ultrasonic. The patients were classified into two groups. Group A (placebo) patients received normal saline in separate syringe. Group B patients received the same solution with nimodipine in a separate syringe at the dose of 10 ml/h (5 ml Brinal nail, Simeute, Egypt). All solution to be injected and adjuvant drugs were prepared by an independent anesthesiologist. After performance of the nerve block. The following parameters were observed: onset time of sensory blockade (time between injection and total abolition of pin pric response) patients were evaluated every 5 min by the pinprick test, duration of sensory blockade (time between onset and return of pin pric response) and duration of analgesia (time between onset of action and onset of pain) and duration of motor blockade (return of complete muscle power). Observations were made every 30 minutes and visual analog scale (VAS) score was done to assess need of analgesia. Tramadol 50 mg was given if VAS more than 4. All observations were made in 4 major nerve distribution areas (Radial, Median, Ulnar and Musculo-cutaneous). Monitored vital parameters (HR, MAP) was recorded preoperatively and every 30 min intraoperative and postoperatively at (1, 2, 6, 12 and 24 hours). Postoperatively, patients were asked to quantify their pain on integer visual analogue pain score between 0 and 10, with 0 representing no pain and 10 worst imaginable pains. Pain scores were recorded at 1, 2, 6, 12, and 24 hours after completion of the surgical procedure. Patients were per fuses with 500 ml of lactated ringer's solution.

The power of this clinical trial was retrospectively calculated using G power analysis program version 3 (Buchner A, etal) using post-hoc power analysis type II error protection of 0.05 and effect size conversion of 0.8, total sample size of 40 patients 20 patients in each group produced a power of 0.79

The statistical analysis of data done by using excel program for figures and SPSS (SPSS, Inc, Chicago, IL) program statistical package for social science version 16. To test the normality of data distribution one-way ANOVA followed by Tukey–HSD multiple comparison test. The description of the data done in form of mean (±) SD for quantitative data and frequency and proportion for qualitative data. The analysis of the data was done to test significant difference between groups. Any difference or change showing probability (P) less than 0.05 was considered statistically significant at confidence interval 95%.

**Results:**

The two groups were similar in demographic data as regard age, weight and sex (Table 1). All brachial plexus blocks were either done by the author or carried out under his supervision. No failed blocks were reported.

The hemodynamic in form of heart rate and mean arterial pressure in the two groups is given in Fig 1&2. There was significant decrease in mean arterial pressure and increase in the heart rate in the group B in comparison to group A most of times from preoperative to 6 hours postoperative. A marginal decrease in the onset time of sensory block was noticed in group B (22.16±1.47 min) as compared to group A (23.25±1.60 min.), which was statistically not significant (p>0.05). Significant prolongation of the duration of sensory block was observed in group B (180.00±7.07 min) as compared
to group A (156.33±6.05 min) (p<0.05). There was non-significant difference in the duration of analgesia or motor block in the two groups (p > 0.05). (Table 2) Visual analog score at first request to analgesia in both groups is given in (Table 3) there was a marginal decrease in early postoperative in Group B as compared to Group A, which was statistically not significant in all postoperative period. There were no signs of central nervous system or cardiovascular toxicity. No cases reported of clinically relevant diaphragmatic paralysis.

**Fig 1**

![Mean arterial blood pressure](image)

Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD Multiple comparison tests. All values are presented as means ± SD

*Indicates significant change from group A at p < 0.05
Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD. *Indicates significant change from group A at p < 0.05. Multiple comparison tests. All values are presented as ± SD.

Table 1
Demographic data

<table>
<thead>
<tr>
<th>Item</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39±6</td>
<td>40±8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64±8</td>
<td>63±11</td>
</tr>
<tr>
<td>Gender (M/f)</td>
<td>9/11</td>
<td>11/9</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. P<0.05 to be significant. Each group contain 20 patients.
Table 2:
Onset and duration of sensory, motor block and analgesia

<table>
<thead>
<tr>
<th></th>
<th>Group A (placebo)</th>
<th>Group B (nimodipine)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sensory block (min)</td>
<td>23.25±1.60</td>
<td>22.16±1.47</td>
<td>0.201</td>
</tr>
<tr>
<td>Sensory duration (min)</td>
<td>156.33±6.05</td>
<td>180.00±7.07</td>
<td>0.001*</td>
</tr>
<tr>
<td>Duration of analgesia (min)</td>
<td>300.50±34.68</td>
<td>307.00±36.89</td>
<td>0.660</td>
</tr>
<tr>
<td>Duration of motor blockade (min)</td>
<td>174.83±11.26</td>
<td>174.16±12.31</td>
<td>0.938</td>
</tr>
</tbody>
</table>

Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD multiple comparison test. All values are presented as means ± SD.

Table 3: Visual Analog Score

<table>
<thead>
<tr>
<th></th>
<th>Group A (placebo)</th>
<th>Group B (nimodipine)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hr</td>
<td>3.00±0.894</td>
<td>2.83±0.752</td>
<td>0.695</td>
</tr>
<tr>
<td>2nd hr</td>
<td>4.66±0.81</td>
<td>4.16±1.169</td>
<td>0.203</td>
</tr>
<tr>
<td>12th hr</td>
<td>5.33±0.81</td>
<td>4.33±1.211</td>
<td>0.144</td>
</tr>
<tr>
<td>24th hr</td>
<td>4.83±1.169</td>
<td>4.00±1.154</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Statistical analysis was carried by one-way ANOVA followed by Tukey–HSD multiple comparison test. All values are presented as means ± SD.

p < 0.05 is considered significant
Each group contain 20 patients.
Discussion:
Our study showed that there was significant prolongation of the duration of sensory block associated with marginal decrease in the onset time of this block in the group receiving nimodipin in addition to lidocaine.
Nowycky et al (1985), reported the evidence of three distinct types of calcium channels in sensory neurons namely L, T, and N type. Of these L and N type of channels have a significant role in regulating neurotransmitter release from neurons. The N type has much more potent antinociceptive effects than L type. N type channel blockers were not clinically suitable for use because of their severe neurotoxicity. Harra et al (1998) showed that L type channel blockers verapamil and diltiazem produced both somatic and visceral pain relief in a dose dependent manner suggesting the relevance of L type channel blockers in pain management. In rats, Ca channel blockers given intrathecally potentiated spinal anesthesia produced by lidocaine or tetracaine. Intrathecal Ca channel blockers alone did not produce motor or sensory block but in combination with lidocaine or tetracaine, the block produced was more potent and of longer duration than that produced by the local anesthetic alone (Fassoulaki et al, 1998). Iwasaki and colleagues demonstrated in rats that local sensory block produced by lidocaine injection at the tail base was potentiated by verapamil, diltiazem and nicardipine in a dose-dependent manner (Iwasaki et al, 1996).
The most common side effects of systemic L-type calcium channel blockers are attributable to excessive vaso/dilatation. Diltiazem and verapamil are less potent vasodilators than other L-type calcium channel blockers, e.g. the dihydropyridines (Nitahara et al, 2003). Peripheral nerve blocks offer the potential benefits of prolonged analgesia with fewer side effects, greater patient satisfaction, and faster functional recovery after surgery (Liu and Salinas, 2003). Because calcium channel blockers are known to potentiate the actions of local anesthetics and opioids, investigators have evaluated them as an adjunct for brachial plexus blockade. Brachial plexus administration of verapamil 2.5 mg increased the duration of surgical anesthesia by approximately 90 minutes when added to lidocaine with epinephrine in axillary block (Reuben and Reuben, 2000).
In the present study, there were significant hemodynamic alterations during the studied time for intraoperative and 12 hours postoperatively, as it is well known that the systemic administration of calcium channel blockers causes vasodilatation and myocardial depression leading to hypotension and bradycardia. On the other hand, there was a statistically significant prolongation of duration of sensory block was detected in group B as compared with group A; These results coincides with the finding by (Lalla et al 2010) who found a significant prolongation of analgesia and sensory block duration in the group receiving a combination of morphine and calcium channel blockers added to lidocaine during brachial plexus block. Calcium channel blockers inhibit various ionic processes and its analgesic properties are complex. It blocks the slow inward trans-membrane ionic current carried by calcium and/or sodium in cardiac and vascular smooth muscle. It also induces fast channel blocking effect similar to local anesthetics (Reuben and Reuben, 2000).
Nimodipine is a dihydropyridine calcium channel antagonist, which binds to the L-type voltage gated calcium channel. It crosses the blood-brain barrier and is demonstrably effective in the prevention of secondary ischemic neurological damage after subarachnoid hemorrhage (Allen et al, 1983). Some researchers have suggested that the analgesic effect of calcium channel blockers mainly as nimodipine is centrally and not peripherally mediated. Choe et al (1998) demonstrated that addition of calcium channel blockers to bupivacaine administered epidurally resulted in less postoperative analgesic requirement. Delpozo et al (1990) found that subcutaneous calcium channel blockers failed to exhibit anti-nociceptive effects, but was clearly analgesic when administered by intracerebroventricular route in rats. Perhaps the analgesic effect of calcium channel blockers in our study was short lived and masked by local anesthetic effect of lignocaine/ bupivacaine.

Conclusion:
The present study showed that the addition of nimodipine as calcium channel blocker to local anesthetic solution in performing brachial plexus block can modify the action of the local anesthetic.

References:

Although in our study it did not significantly modify the onset or duration of analgesia, there was a statistically significant increase in duration of sensory blockade with minor effect on cardiovascular and respiratory system of the patients.


Lalla RK, Anant S, Nanda HS: Verapamil as an Adjunct to Local Anaesthetic for Brachial Plexus Blocks. MJAFI (2010); 66 : 22-24