THE EFFECT OF NITROGLYCERIN AS AN ADJUVANT TO LIDOCAINE IN INTRAVENOUS REGIONAL ANESTHESIA

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Implication Statement

The present study is the second to assess nitroglycerin as a new adjuvant for intravenous regional analgesia. Its addition to lidocaine, nitroglycerin appears to shorten the sensory and motor block onset time in closed reduction of forearm fractures and provides acceptable analgesia for 24 hours after operation.

Abstract

Purpose: The disadvantages of intravenous regional anesthesia (IVRA) include slow onset, poor muscle relaxation, tourniquet pain, and rapid onset of pain after tourniquet deflation. In this randomized, double-blind study, we evaluated the effect of nitroglycerin (NTG) in quality improvement when added to lidocaine in IVRA.

Methods: Forty-six patients (20-50 yrs), were randomly allocated in two equal groups. Under identical condition, the control group received a total dose of 3mg/kg of lidocaine 1% diluted with saline, and the study group received an additional 200 µg NTG. Vital signs and tourniquet pain, based on visual analog scale (VAS) score were measured and recorded before and 5, 10, 15, 20, and 30 min after anesthetic solution administration. The onset times of sensory and motor block were measured and recorded in all patients. After the tourniquet deflation, at 30 min and 2, 4, 6, 12 and 24h, VAS score, time to first analgesic requirement, total analgesic consumption in the first 24 h after operation, and side effects were noted.

Results: The sensory and motor block onset time were shortened in study group (2.61 vs. 5.09 and 4.22 vs. 7.04 min, respectively) (p <0.05). The recovery time of sensory and motor block and onset of tourniquet pain were also prolonged (7.26 vs. 3.43, 9.70 vs. 3.74 and 25 vs. 16.65min., respectively) (p <0.05). Analgesia time after tourniquet deflation was prolonged and tourniquet pain intensity was lowered in study group (p <0.05). Intraoperative fentanyl and meperidine requirement during first postoperative day and pain intensity at 4, 6, 12 and 24 hr postoperatively were lower in the study group (p <0.05). There were no significant side effects.

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**Conclusion:** The NTG adding to lidocaine in intravenous regional anesthesia shortens onset times of sensory and motor block and decreases the tourniquet and postoperative pain, without any side effect.

**Keywords:** Intravenous regional anesthesia, Nitroglycerin, Lidocaine.

**Introduction**

The technique of intravenous regional anesthesia (IVRA) was first introduced by German surgeon August Bier in 1908\(^1\). It consists of injecting local anesthetic solutions into the venous system of an upper or lower extremity that has been exsanguinated by compression or gravity and that has been isolated by means of a tourniquet from central circulation. The resultant anesthesia is produced by direct diffusion of local anesthetic from the vessels into the nearby nerves. This technique is easy, cost-effective and its efficacy in emergency and out patients setting has been proved\(^2\).

Complications of IVRA are a few and mostly limited to systemic toxicity from local anesthetic that is related to problems with the technique. The risk mainly comes from an inadequate tourniquet application or equipment failure at the beginning of the procedure.

Its slow onset, tourniquet pain during the procedure, limited operating time (<1 h), possible nerve damage and insufficient postoperative analgesia are among a few disadvantages of this technique.

Analgesic effects of transdermal Nitro-glycerin (NTG) have been reported in several studies\(^3,4,5,6,7,8\) and recently Nitro-glycerin has been used as an adjuvant in IVRA and its effects on tourniquet pain and intraoperative and postoperative analgesia were promising\(^9\). We decided to conduct a similar study in patients scheduled for close reduction of forearm fracture and evaluate the duration of analgesic effect for 24 hours postoperatively.

The essence of science implies that study findings must be replicated in a different study before firm conclusion can be drawn. Thus, the present study is the second to assess the efficacy and safety of using Nitroglycerin in IVRA as an adjuvant.

**Methods and Materials**

Informed patient consent and ethical and research committees approval were obtained. In a prospective, randomised double-blinded study, forty six ASA I – II patients age 20-50 years scheduled for closed reduction of forearm fractures were included in two equal groups. The sample size was calculated based on a type I error of \(\alpha = 0.05\), \(p_1/p_2\) equal to 2.75 and \(p_2 = 0.15\). Enrollment of 23 patients in each group was required. Patients with sickle cell anemia, Reynaud disease, and history of drug allergy, antihypertensive drug and NTG consumption were excluded.

In operating room, patient’s vital signs (arterial blood pressure, heart rate, \(\text{SpO}_2\), ECG) were monitored by Datascope passport 2. Premedication for both groups consisted of IV midazolam 0.15 mg/kg and 1 µg/kg fentanyl. An intravenous cannula (gauge 20) was placed in a distal vein of the hand in preparation for IVRA. The arm was elevated for six minutes then a rubber Esmarch bandage was wound around the arm spirally to exsanguinate the arm. A double pneumatic tourniquet was placed around the upper arm and the proximal cuff was inflated based on LOP (Limb Occlusion Pressure) with safety margin of about 50 mmHg.

Absence of radial pulse and loss of pulse oximetry tracing was considered as an adequate isolated circulation of the arm. In study group IVRA was administered with 200 µ NTG, (Trinitrosan 5 mg/1ml, Merck KGaA, Darmstadt, Germany) plus 3 mg/kg lidocaine (LIGNODIC\(^\circ\). Lidocaine 1%, Caspian Tamin Pharmaceutical Co., Rasht-Iran)) diluted with saline to a total volume of 40 ml. In control group 3 mg/kg lidocaine diluted with saline to the same volume was injected over 60 seconds by an anesthesiologist blinded as to group assignments.

To assess the sensory block, pinprick with a 22 gauge short-beveled needle was performed in the dermatomal sensory distribution of median, ulnar and radial nerves. Complete motor block was noted when no voluntary movement in patients wrist and fingers was possible. Sensory and motor block onset times were recorded.

After the onset of sensory and motor block, distal cuff of tourniquet was inflated to 250 mmHg and the
proximal cuff was deflated. BP, HR, SpO₂ and Visual Analog Scale (VAS) scores (0 = no pain and 10 worst pain) was monitored before and at 5, 10, 15, 20, 25, 30 min after tourniquet deflation. When pain was >3 on the VAS scale, patients were given intravenous fentanyl 1 µg/kg. Times and total dose of intraoperative fentanyl were recorded. Tourniquet was not deflated sooner than 30 min. At the end of surgery through cyclic deflation technique, it was deflated. Sensory and motor block recovery time was noted. Vital signs and pain intensity (VAS) were monitored 30 min and 2, 4, 6, 12 and 24 h postoperatively. Patients with VAS >3 received 30 mg IM meperidine and the total dose of meperidine in first 24 h after surgery was recorded. Quantitative and qualitative data were analyzed by Independent sample student’s t-test and Fischer’s exact χ² test respectively.

**Results**

The demographic data in both groups were similar and no significant difference was noted (p >0.05, Table 1).

![Table 1: Patient Characteristic](image)

The same surgeon performed surgical procedure (closed reduction of forearm fracture). There was no statistically significant difference in vital signs (MAP, HR) in both groups intraoperatively and after tourniquet deflation (p >0.05).

The onset time of sensory and motor block in the study group were shorter (2.65 vs. 5.09 and 4.22 vs. 7.04 min, respectively, p <0.05) and the recovery time for sensory and motor block were slower (7.26 vs. 3.43 and 9.07 vs. 3.74 min, respectively) (p <0.05). The study group took longer time to complain of tourniquet pain and analgesia lasted longer in study group (25.00 vs. 16.65 and 130.32 vs. 38.21 min, respectively) (p <0.05, Table 2).

Although there was no significant difference in pain intensity 15 minutes from the start of operation, yet during the next 15 minutes pain intensity and tourniquet pain, determined by VAS was lower in study group compared to control group (p <0.05).

The average dose of intraoperative IV fentanyl in study group was less than control one (18.26 vs. 78.04 micg, respectively, p <0.05) (Table 3). The average pain intensity in 4, 6, 12 and 24 hour postoperation in study group was less compared to control group (p <0.05) but maximum pain intensity in first day postoperatively as determined by VAS, was similar in both groups (p <0.05). In study group intramuscular meperidine injection (35.42 mg) was also less compared to control group (55.65 mg) (p <0.05) (Table 3).

No adverse effect was noted in both groups.

**Discussion**

The results of this study suggest that the addition of NTG to lidocaine for IVRA in closed reduction of forearm fractures, without any notable side effects, improved the onset and duration of sensory and motor block and anesthesia quality, decreased tourniquet pain in terms of both onset and duration and intraoperative and postoperative analgesic consumption.

Several studies have reviewed the use of adjuncts (i.e., opioids, non steroid anti-inflammatory drugs, α2 agonists, neostigmine, muscle relaxants, magnesium and sodium bicarbonate) to intravenous regional anesthesia. Selda Sen et al performed the first study on adding NTG to IVRA for hand and forearm surgery such as tendon release, trigger point and carpal...
effects and analgesia by blocking hyperalgesia and the neurogenic component of inflammatory edema through NO production.

Direct stimulation of peripheral fibers, similar to locally applied acetylcholine is another possible mechanism for analgesic effect of NTG. The above mentioned mechanisms or combination of them, might contribute to the analgesic effects of NTG added to lidocaine in IVRA.

**Conclusion**

The results of this study suggest that with addition of NTG to lidocaine in IVRA improves the quality of the block, decreases tourniquet pain and opioid consumption in first postoperative day. Further study might be undertaken to evaluate the local anesthetic sparing effect of NTG in IVRA.

<table>
<thead>
<tr>
<th>Pain after tourniquet deflation (VAS) 5 min</th>
<th>Study G (±SD)</th>
<th>Control G (±SD)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.43±0.21</td>
<td>0</td>
<td>0.328</td>
<td></td>
</tr>
<tr>
<td>Pain after tourniquet deflation (VAS) 10 min</td>
<td>0.43±0.21</td>
<td>0.09±0.3</td>
<td>0.561</td>
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<tr>
<td>Pain after tourniquet deflation (VAS) 15 min</td>
<td>0.43±0.21</td>
<td>3.22±2.07</td>
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<tr>
<td>Pain after tourniquet deflation (VAS) 20 min</td>
<td>1.04±1.3</td>
<td>3.26±0.69</td>
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<tr>
<td>Pain after tourniquet deflation (VAS) 30 min</td>
<td>1.96±1.4</td>
<td>3.50±0.7</td>
<td>†</td>
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<tr>
<td>Average tourniquet pain</td>
<td>0.63±0.52</td>
<td>1.98±0.52</td>
<td>†</td>
</tr>
<tr>
<td>Maximum tourniquet pain</td>
<td>2.00±1.45</td>
<td>4.35±0.77</td>
<td>†</td>
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<tr>
<td>Onset of tourniquet pain (min)</td>
<td>25.00±2.09</td>
<td>16.65±4.64</td>
<td>†</td>
</tr>
<tr>
<td>Average fentanyl consumption (µg)</td>
<td>18.26±29.29</td>
<td>78.04±50.98</td>
<td>†</td>
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<td>Pain intensity 4h postoperation (VAS)</td>
<td>2.93±0.61</td>
<td>3.68±0.71</td>
<td>†</td>
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<td>Pain intensity 6h postoperation (VAS)</td>
<td>2.65±0.56</td>
<td>3.33±0.60</td>
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<td>Pain intensity 12h postoperation (VAS)</td>
<td>2.33±0.52</td>
<td>2.96±0.52</td>
<td>†</td>
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<tr>
<td>Pain intensity 24h postoperation (VAS)</td>
<td>1.91±0.45</td>
<td>2.52±0.45</td>
<td>†</td>
</tr>
<tr>
<td>Maximum postoperative pain intensity (VAS)</td>
<td>4.52±0.66</td>
<td>4.78±0.90</td>
<td>0.271</td>
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<td>Meperidine consumption 24h postoperation (mg)</td>
<td>35.43±10.10</td>
<td>55.65±22.02</td>
<td>†</td>
</tr>
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</table>

† p-value <0.0001.  * Independent Samples T-Test.
References
