**The Effect of Adding Nitroglycerine as an Adjuvant to Lidocaine on the Quality of Intravenous Regional Anesthesia**

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**Abstract**

**Introduction:** Intravenous regional anesthesia (IVRA) of the upper limb is a simple and effective technique that can be used at all age groups, and its cost is low. One of its limitations is lack of postoperative pain relief after tourniquet deflation. Several pharmacological adjuvants (drugs) have been added to lidocaine to improve postoperative analgesia after IVRA, such as opioids, tramadol, nonsteriodal anti-inflammatory drugs, clonidine, dexmedetomidine and other drugs.

**Methods:** We used nitroglycerine (NTG) as an adjuvant to lidocaine to evaluate its effect on the quality on IVRA and postoperative pain relief. After informed written consent and ethical committee approval, forty patients undergoing short hand and forearm surgery under IVRA were randomly assigned into two equal groups. Group I (control group) received 3 mg/kg of lidocaine 2% diluted with saline to a total volume of 40 ml for IVRA. Group II (NTG group) received the same dose of lidocaine to which we added 100 µg nitroglycerine diluted to the same volume of solution. Tourniquet pain as well as hemodynamic parameters were measured and recorded 2, 5, 10,15,20,30 and 40 minutes after tourniquet inflation. Onset of sensory and motor block was recorded in each patient. At the end of surgery and after tourniquet deflation, sensory and motor recovery times were tested at 5, 10, 15, 20 and 30 minutes then every 1 hour till full recovery.Visual analogue scale (VAS) was used for assessment of postoperative pain at 15; 30 minutes, 1 hour, and then every 2 hour for 24 hours. Time for the first analgesic requirement was observed and recorded. Postoperative analgesia was achieved by using diclofenac 75mg. i.m, oral diclofenac 50mg. was given if needed in the first 24 hours (if VAS>3). Side effects were noted and recorded.

**Results:** There was significant shortening in VAS score of tourniquet pain in NTG group compared to control group (P<0.05). Sensory and motor block onset times were less in NTG in comparison with control group (3.95 ± .82 vs 5.60 ± 1.0 min ) for sensory,( 6.35 ± .98 vs 7.65 ± 1.20 min) for motor block. Sensory and motor recovery times were prolonged in NTG group compared to control group ( 7.75 ± 2.7 vs 3.8 ± 1.2 min ) for sensory, (12.60 ± 3.76 vs 5.95 ± 1.7min ) for motor recovery. Postoperative analgesia after tourniquet deflation was prolonged with statistically significant difference in VAS scores in all reading of first four hours postoperatively. Time (in minutes) to the first analgesic requirement time was prolonged in NTG group compared to control group (206 ± 33 vs 62 ± 20 min). Diclofenac consumption was much less in NTG group than in control group (127 ± 27 vs 165± 27 mg). No side effects were observed in any patients of either group.

**Conclusion:** addition of nitroglycerine to lidocaine in intravenous regional anesthesia improves sensory and motor block and decreases tourniquet pain and prolongs postoperative analgesia with no side effects.

**Introduction:**

Intravenous regional anesthesia (IVRA) is one of the simplest forms of regional anesthesia and has the most frequent success **[1]**. Lidocaine 0.5%–1% is one of the commonly used local anesthetic for IVRA [**2**].

Intravenous regional anesthesia has their limitations which are tourniquet pain and its inability to provide postoperative analgesia **[3]**. To improve block quality, prolong postoperative analgesia, and decrease tourniquet pain, different additives been added to local anesthetics, there are tramadol **[4]**, clonidine **[5**], dexmedetomidin **[6]** and dexamethasone **[2, 4]** added to the local anesthetics. Also various nonsteroidal anti-inflammatory drugs have been demonstrated to enhance analgesia such as ketorolac **[7]** and opioids **[8]**. Literatures on the effect of adding nitroglycerine as an adjuvant to lidocaine for IVRA are few.

Nitroglycerine is metabolized to nitric oxide (NO) in the cell. NO causes an increase in the intracellular concentration of cyclic guanosine monophosphate, which produces pain modulation in the central and peripheral nervous system **[9]**.

The aim of this study is to evaluate the effect of adding nitroglycerine to lidocaine for IVRA on tourniquet pain, sensory and motor block onset and recovery times and postoperative pain.

**Methods:**

after obtaining institutional ethical committee approval and written informed consent, 40 patients between 20-50 years; undergoing hand and forearm surgery (carpal tunnel, trigger finger, and tendon release or repair, simple ganglion removal, fracture of ulna or radius fixation) under IVRA; were the subject of the study. Patients having sickle cell anemia, history of drug allergy and Reynaud's or other vascular disease were excluded from the study. Pre-operative assessment (history, examination and investigations) were done and VAS is explained to all patients, routine monitoring intraoperatively in the form of electrocardiography (ECG), automated noninvasive blood pressure measurement and pulse oximetry to detect heart rate (HR), mean arterial blood pressure (MAP) and oxygen saturation (SpO2%) were applied to every patient. IV cannulae were placed; one was in the dorsum of operative hand and the other in the opposite hand for fluid infusion or drugs administration. The operative arm was elevated then squeezed with bandage; a tourniquet was then placed around the upper arm. Absence of radial pulse and loss of pulse oximetry in the index finger of the operative hand were checked before giving IVRA. In control group (group I) received IVRA with 3mg/kg of lidocaine 2% diluted with saline to a total volume of 40 ml, study group (group II) received IVRA with (3mg/kg) of lidocaine 2% with 100 µg nitroglycerine diluted with same volume. Sensory block was assessed by a pinprick with needle. Motor block was assessed by asking the patient to flex and extend wrist and fingers, complete motor block was determined as voluntary movement lost. The operative tourniquet was applied after complete sensory and motor block, and the proximal tourniquet was released and surgery was started. The operative tourniquet was released not before 30 min after its application. Intraoperative Tourniquet pain as well as hemodynamic parameters (MAP, HR, and SpO2%) were measured and recorded 2, 5,10,15,20,30 and 40 minutes after tourniquet inflation. Onset of sensory and motor block was recorded in each patient. At the end of surgery and after tourniquet deflation, sensory and motor recovery times were tested at 5, 10, 15, 20 and 30 minutes then every 1 hour till full recovery, sensory recovery time was evaluated by pinprick and motor block recovery time was evaluated by movement of fingers. VAS was used for assessment of postoperative pain at 15; 30 minutes, 1 hour, and then every 2 hour for 24 hours. Time for the first analgesic requirement was observed and recorded. Postoperative analgesia was achieved by using intramuscular diclofenac 75mg, oral diclofenac 50mg was given if needed in the first 24 hours (if VAS>3). The total diclofenac consumption was recorded in the first 24 hours postoperatively. Side effects of local anesthetic toxicity or nitroglycerine such as tinnitus, tachycardia, hypotension, headache, nausea, or other side effects were noted and recorded.

The data were analyzed to detect the significant statistical difference using SPSS statistical package version (16). Descriptive statistics, qualitative data were expressed in number and percent while quantitative data were expressed in mean (X), standard deviation (SD). The analytical statistics, following tests were done; student t test and Chi square test (X2) **[10]**.

**Results:**

There were no significant differences in age, sex, body weight ASA classification and the tourniquet time between the groups as shown in table (1).

***Table (1).Patient's demographic data, ASA class and* tourniquet time *given as mean (SD*)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Control group** | **Nitroglycerine group** | **P value** |
| **Age(years)** | **36.95± 7.756** | **38.20±8.464** | **>0.05** |
| **Sex(male: female)** | **10:10** | **11:9** | **>0.05** |
| **body weight kg** | **74.25±6.544** | **75.20±7.098** | **>0.05** |
| **ASA I:II** | **15:5** | **15:5** |  |
| **tourniquet time** | **47.50±3.441** | **47.75±6.340** | **>0.05** |

There were no significant differences in preoperative , intraoperative, postoperativeMAP ; HR and SpO2% in NTG group compared to control group (P>0.05); as shown in table (2).

**Table (2): Comparison between Control group & Nitroglycerine group as regards preoperative, intraoperative, postoperative MAP; HR and SpO2 %:**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **MAP (mmhg)** | | **HR (beat/min)** | | **SpO2 %** | | ***P value*** |
| **Control group** | **NTG group** | **Control group** | **NTG group** | **Control group** | **NTG group** |
| **Mean ±SD** | **Mean ±SD** | **Mean ±SD** | **Mean ±SD** | **Mean ±SD** | **Mean ±SD** |
| **Preoperative** | | **94.35±9.778** | **92.05±7.850** | **77.25±6.248** | **76.75±5.486** | **96.45±1.146** | **96.75±.910** | **>0.05** |
| **Intraoperative** | **2 min** | **94.60±9.428** | **89.85±10.505** | **78.40±6.082** | **77.35±5.019** | **97.35±.745** | **97.60±.681** | **>0.05** |
| **5 min** | **94.80±8.989** | **89.75±6.805** | **78.60±6.269** | **76.50±5.206** | **97.45±.510** | **97.55±.686** | **>0.05** |
| **10 min** | **94.75±8.441** | **92.05±8.300** | **78.70±5.921** | **76.85±4.626** | **97.45±.605** | **97.55±.605** | **>0.05** |
| **20 min** | **95.45±9.528** | **90.55±7.571** | **78.35±6.418** | **78.85±4.671** | **97.55±.686** | **97.45±.686** | **>0.05** |
| **30 min** | **95.65±9.783** | **91.45±7.193** | **79.20±6.363** | **79.50±4.174** | **97.20±.616** | **97.50±.688** | **>0.05** |
| **40 min** | **102.25±6.840** | **95.42±7.525** | **82.22±8.333** | **82.82±4.309** | **97.00±.535** | **97.24±.809** | **>0.05** |
| **Postoperative at 30 min** | | **96.00±10.270** | **92.70±7.616** | **80.75±7.203** | **82.35±6.089** | **96.85±.813** | **96.55±.759** | **>0.05** |

The onset of tourniquet pain was prolonged (35.70± 3.90 in NTG group vs 28.90 ± 5.80 min control group) and there was significant shortening in VAS score of tourniquet pain in NTG group compared to control group (P<0.05). There is no incisional pain, ten patients in control group and five patients in nitroglycerine group received pethedine (50 mg) for tourniquet pain. (Table 3)

Sensory block onset times were shorter (3.95 ± .82 vs 5.60 ± 1.046 min) with statistically significant difference (P<0.001) in NTG group when compared to control group , Motor block onset times were shorter and statistically significant in NTG group (6.35 ± .988 min in NTG group vs 7.65 ± 1.2 min in control group , P<0.05), sensory and motor block recovery times were prolonged and statistically significant in NTG group (7.75 ± 2.712 min in NTG group vs 3.80 ± 1.240 min in control group for sensory recovery times and 12.60 ± 3.761min in NTG group vs 5.95 ± 1.701 min in control group for motor , P<0.001). (Table 3)

**Table (3): Comparison between control group & nitroglycerine group as regards onset of tourniquet pain sensory and motor block onset and recovery times:**

|  | **Control group** | | **NTG group** | | **t** | **p** |
| --- | --- | --- | --- | --- | --- | --- |
| **Mean** | **±SD** | **Mean** | **±SD** |
| **Onset of tourniquet pain** | **28.90** | **5.80** | **35.70** | **3.90** | **2.3** | **<0.05** |
| **Sensory block onset times** | **5.60** | **1.046** | **3.95** | **.826** | **5.5** | **<0.001** |
| **Motor block onset times** | **7.65** | **1.226** | **6.35** | **.988** | **3.7** | **<0.05** |
| **Motor block recovery times** | **5.95** | **1.701** | **12.60** | **3.761** | **7.2** | **<0.001** |
| **Sensory block recovery times** | **3.80** | **1.240** | **7.75** | **2.712** | **5.9** | **<0.001** |

Postoperative VAS scores were shorter and statistically significant (P<0.001) in NTG group compared with control group in the first four hour after tourniquet release as VAS scores at 15 min (.75 ± .639 cm in NTG group vs 1.90 ± .641 cm in control group), after thirty minutes (1.45 ±.510 cm in NTG group vs 2.60 ± .940 cm in control group), after two hours (2.30 ± .657 cm in NTG group vs 3.90± .940 cm in control group) and after four hours (3.30± .813 cm in NTG group vs 4.35 ± .801 cm in control group). There was no significant difference at 8, 16, 24 hour (P>0.05). (Table 4)

**Table (4):** **Comparison between Control group & Nitroglycerine group as regards Postoperative visual analog scale (VAS) scores**

|  | | **Control group** | | **NTG group** | | **t** | **p** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Mean** | **±SD** | **Mean** | **±SD** |
| **visual analog scale (VAS)** | **15 min** | **1.90** | **.641** | **.75** | **.639** | **5.7** | **<0.001** |
| **30 min** | **2.60** | **.940** | **1.45** | **.510** | **4.8** | **<0.001** |
| **2 hour** | **3.90** | **.641** | **2.30** | **.657** | **7.8** | **<0.001** |
| **4 hour** | **4.35** | **.801** | **3.30** | **.813** | **4.1** | **<0.001** |
| **8 hour** | **4.15** | **.707** | **2.75** | **.967** | **1.7** | **>0.05** |
| **16 hour** | **4.30** | **.733** | **3.95** | **.887** | **1.4** | **>0.05** |
| **24 hour** | **4.25** | **.550** | **4.05** | **.826** | **0.8** | **>0.05** |

The first postoperative analgesic requirement time was prolonged and statistically significant in NTG group (206.84 ± 33.00 min in NTG group vs 62.50 ± 20.03 min in control group, P<0.001). (Table 5)

Diclofenac consumption was smaller and statistically significant in NTG group in first postoperative twenty-four hours difference between the two groups (127.50 ± 27.980 mg in NTG group vs 165.00 ± 27.386 mg in control group, P<0.001). (Table 5)

**Table (5): Comparison between Control group & Nitroglycerine group as regards first analgesic requirement time (min) and diclofenac consumption (mg)**

|  | **Control group** | | **NTG group** | | **t** | **p** |
| --- | --- | --- | --- | --- | --- | --- |
| **Mean** | **±SD** | **Mean** | **±SD** |
| **First analgesic requirement time (min.)** | **62.50** | **20.033** | **206.84** | **33.00** | **16.6** | **<0.001** |
| **Diclofenac consumption (mg)** | **165.00** | **27.38** | **127.50** | **27.98** | **4.3** | **<0.001** |

There was no significant difference between the two groups in side effects (10% in control group vs 30 % in nitroglycerine group, P>0.05). Two patients in control group developed transient tinnitus while two patients developed transient tachycardia at tourniquet release, one patient developed transient slight headache, and three patients develop venous congestion in operative side in nitroglycerine group.

**Discussion:**

The results of this study revealed that addition of nitroglycerine to lidocaine in intravenous regional anesthesia improves sensory and motor block and decreases tourniquet pain and prolongs postoperative analgesia with no significant side effects.

Hemodynamic parameters in this study show no significant difference, this is in agreement with ***Selda Sen et al*** **[11]**and ***Abbasivash et al*. [12]** who studied the effect of adding NTG (200 µg) to lidocaine (3mg/kg) for IVRA and they found that MAP, HR, and SpO2% were show no significant difference between the groups at intraoperative or postoperative period (*P* > 0.05).

There was significant shortening in VAS score and prolonged onset of tourniquet pain in NTG group compared to control group (P<0.05)***,*** which agree with ***Selda Sen et al*** who reported that NTG shortenedVAS scores of tourniquet pain (*P* = 0.023), ***Abbasivash et al*** found that onset of tourniquet pain was prolonged in NTG group compared with control group (25 vs. 16.65min., respectively, P <0.05). This effect may be due to anti-inflammatory effects and analgesia induced by nitric oxide generators which block hyperalgesia and the neurogenic component of inflammatory edema **[13]** or through direct stimulation of peripheral fibers similar the actions of locally applied acetylcholine **[14]**.

Sensory and motor block onset times were less and recovery times were prolonged in NTG group compared to control group in this study, ***Selda Sen et al*** reported that NTG shortened sensory and motor blockonset time (3.2 ± 1.1 versus 4.5 ± 1.2 min; and 3.3 ± 1.6 versus 5.2 ± 1.8; *P* = 0.009in group NTG and control group, respectively), prolonged sensory andmotor block recovery times (6.8 ± 1.6 versus 3.1 ±1.2 min and 7.3 ± 1.3 versus 3.6 ±0.8 *P* < 0.0001 in group NTG and control group, respectively) and ***Abbasivash et al****.* found that sensory and motor block onset time were shortened in NTG group (2.61 vs.5.09 and 4.22 vs. 7.04 min, respectively; P <0.05), prolonged sensory andmotor block recovery times (7.26 vs. 3.43, 9.70 vs. 3.74 min., respectively; P <0.05). The rapid onset of sensory and motor block explained by the strong vasodilator effect of NTG that causes rapid distribution of lidocaine to nerves **[11]**.

***Elmetwaly et al.* [15]** compared the effect of adding ketamine or nitroglycerine (NTG) as adjuvants to lidocaine for IVRA; they reported that both ketamine and nitroglycerine shorten sensory and motor blocks. NTG has a rapid onset of sensory and motor blocks than ketamine which could be also explained by the its strong vasodilator effect while ketamine produced better tolerance to tourniquet than NTG due to antagonism of NMDA receptors in peripheral nerves**[16]**.

***Turan A et al*. [17]** investigated the effects of transdermal NTG 10 mg which applied 2 hours before giving IVRA using 2% prilocaine (3 mg/kg), they found that transdermal NTG shorten onset of sensory block and motor block recovery time was significantly longer (p<0.05), and this agrees with the result of this study but they differ in using prilocaine and transdermal patch instead of lidocaine and intravenous NTG, also they did not evaluate postoperative pain.

***Marashi et al.* [18]**disagree with the results of previous investigators or this study as they studied the analgesic effect of intravenous neostigmine (0.5 mg) added to lidocaine and transdermal NTG (5mg) as adjuvants to IVRA, transdermal NTG was applied at the proximal forearm above surgical site. Ten minutes was allowed after injection of local anesthetic for block onset. After 15 min of injection in all patients, distal tourniquet was inflated. They reported that there were no significant differences in severity of tourniquet pain, tourniquet pain onset when transdermal NTG used as an adjuvant to lidocaine with or without neostigmine. This may be due to operation started after 15 min of injection while transdermal NTG patch vasodilator effect takes 20-40 minutes to start which is not strong or rapid as intravenous NTG **[19]**.

Postoperative analgesia after tourniquet deflation was prolonged with statistically significant difference in VAS scores in all reading of first four hours postoperatively in NTG group (P<0.001), this is in agreement with ***Selda Sen et al*.** who reported that VAS scoreswere lower in group NTG after tourniquet release and in thepostoperative period (*P* = 0.001), also ***Abbasivash et al****.* reported that pain intensity at 4, 6, 12 and 24 hr postoperatively were lower in the study group (p <0.05).

The first analgesic requirement time was prolonged and diclofenac consumption was much less in NTG group than in control group in our study, this is in agreement with ***Selda Sen et al*.** who found first analgesic requirement time was longer and postoperative analgesic requirements were significantly smaller in group NTG than in control group (*P* < 0.0001). Also ***Abbasivash et al***, reported that analgesia time after tourniquet deflation was prolonged NTG group (p <0.05).This may be due to pain modulation in the central or peripheral nervous system **[9].**

Nitroglycerine may causedose-dependent side effects such as hypotension, tachycardia,or headache **[20**] and has a very short half-life [[**9**](file:///F:\sabra%20resala\916.htm#R15-43)]. In this study, there was statistically no significant difference between the two groups in side effects due to the use of small dose of NTG and tourniquet release not done before 30 min.

**Conclusion:**

The addition of nitroglycerine to lidocaine in intravenous regional anesthesia improves sensory and motor block, decreases tourniquet pain, prolongs sensory and motor block recovery times and postoperative analgesia and decreases analgesic consumption with no significant side effect.

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