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The analgesic effect of three different doses of nitroglycerine when added to lidocaine for intravenous regional anesthesia in trauma patients

Travma hastalarında intravenöz rejyonel anestezi için lidokaine eklenmesi durumunda üç farklı nitrogliserin dozunun analjezik etkisi

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BACKGROUND

Nitroglycerine (NTG) has analgesic properties. The aim of the present study was to assess the analgesic effect of three different doses of NTG (200 µg, 300 µg and 400 µg) when added to lidocaine in intravenous regional anesthesia (IVRA) in trauma patients.

METHODS

One hundred patients undergoing hand surgery were randomly allocated to four groups to receive 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 mL in the control group (Group LS, n = 25) or 200, 300, 400 µg NTG plus 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 mL in the NTG group (Groups LN1, LN2, LN3 respectively; n = 25 in each group). Before and after the tourniquet application, hemodynamic variables, tourniquet pain, sedation, and analgesic use were recorded.

RESULTS

Sensory and motor block onset times were significantly shorter in the LN3 group compared with Groups LN1, LN2, and LS ($p<0.05$). Sensory and motor block recovery times were statistically prolonged in the LN3 group when compared with Groups LN1 and LS ($p<0.05$). Postoperative visual analogue scale (VAS) scores were significantly lower at 2, 4, 8, 12, and 24 hours after tourniquet release in Group LN3 compared with Group LS ($p<0.05$).

CONCLUSION

The addition of 400 µg NTG to lidocaine in IVRA shortens the onset of sensory and motor block in trauma patients and improves the quality of anesthesia and perioperative analgesia better than the addition of 200 µg or 300 µg NTG, without causing side effects.

Key Words: Anesthetic techniques; lidocaine; nitroglycerin; tourniquet pain; trauma patients.

AMAÇ

Nitrogliserin (NTG), analjezik özelliklere sahiptir. Mevcut çalışmanın amacı, travma hastalarında intravenöz rejyonel anestezide (IVRA) lidokain eklendikten sonra üç farklı NTG dozunun (200 µg, 300 µg ve 400 µg) analjezik etkisini değerlendirmektir.

GEREÇ VE YÖNTEM

El cerrahisi uygulanan 100 hasta rastgele dört gruba ayrıldı: Kontrol grubunda serum fizyolojik ile toplam 40 mL'lik bir doza dilüe edilen 3 mg/kg %2 lidokain (Grup LS, n=25) veya NTG grubunda serum fizyolojik ile toplam 40 mL'lik bir doza dilüe edilen 200, 300, 400 µg NTG + 3 mg/kg 2% lidokain (sırasıyla Grup LN1, Grup LN2, Grup LN3; her bir grupta n=25) uygulandı. Turnike uygulamasından önce ve sonra, hemodinamik değişkenler, turnike ağrısı, sedasyon ve kullanılan analjezik kullanımı kaydedildi.

BULGULAR

Duysal ve motor bloğun başlama zamanları, LN1, LN2 ve LS gruplarına göre LN3 grubunda anlamlı şekilde daha kısaydı ($p<0,05$). Duysal ve motor bloğun geriye dönme zamanları, LN1, LN2 ve LS gruplarına kıyasla LN3 grubunda anlamlı şekilde daha uzundu ($p<0,05$). Ameliyat sonrası vizüel analog skala (VAS) skorları, LS-grubuna kıyasla LN3 grubunda turnikenin gevşetilmesinden 2., 4., 8., 12. ve 24. saat sonra anlamlı şekilde daha düşüktü ($p<0,05$).

SONUÇ

IVRA'da lidokaine 400 µg NTG'nin eklenmesi, 200 µg veya 300 µg NTG'nin eklenmesine göre, travma hastalarında yan etkilere yol açmaksızın, duysal ve motor bloğun başlama zamanını kısaltır, anestezi kalitesini ve perioperatif analjeziyi artırır.

Anahtar Sözcükler: Anestetik teknikler; lidokain; nitrogliserin; turnike ağrısı; travma hastaları.

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The majority of patients with trauma have tendon rupture of the hands or feet. Furthermore, there are crush injuries in the hands and feet that require orthopedic surgeries. Relieving postoperative pain is an important issue that must be considered.

Intravenous regional anesthesia (IVRA) is a technically simple, reliable and cost-effective method of regional anesthesia for short operative procedures of the extremities performed on an ambulatory basis in trauma patients.[1,2] IVRA has disadvantages that include local anesthetic (LA) toxicity, slow-onset poor muscle relaxation, tourniquet pain, and the inability to provide prolonged postoperative analgesia.[1,3]

Different additives such as opioids, tramadol, nonsteroidal antiinflammatory drugs, dexmedetomidine, and muscle relaxant have been combined with LAs to improve block quality, prolong post-deflation analgesia and decrease tourniquet pain.[1,3,4]

Sen and colleagues[5] showed that the addition of 200 µg nitroglycerine (NTG) to lidocaine for IVRA improves sensory and motor block, tourniquet pain and postoperative analgesia without side effects. They emphasized that more studies with different doses must be performed to determine a relevant conclusion before the routine use of NTG. We thus designed the present study to evaluate the effect of three different doses of NTG (200 µg, 300 µg and 400 µg) on sensory and motor block onset and recovery time, the quality of anesthesia, intraoperative and postoperative hemodynamic variables, intraoperative and postoperative pain, tourniquet pain, and the side effects of NTG when added to lidocaine for IVRA in trauma patients.

MATERIALS AND METHODS

One hundred American Society of Anesthesiologists (ASA) physical status I-II trauma patients, aged 18-65 years old, scheduled for elective hand or forearm surgery gave written informed consent to participate in this randomized prospective double-blind study, which was approved by the Ethics Committee of our institute. Exclusion criteria were patients with Reynaud disease or sickle cell anemia and those with a history of allergy to any drug used.

After arrival of patients to the operating room, mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2) and heart rate (HR) were monitored.

The operative arm was elevated for 3 minutes (min), after which it was exsanguinated with an Esmarch bandage. A 10 cm pneumatic padded double-tourniquet was then placed around the upper arm and the proximal cuff was inflated to 250 mmHg. Circulatory isolation of the arm was confirmed by skin blanching, absence of radial pulse and loss of pulse oximetry tracing in the ipsilateral index finger.

A randomization list was generated and identical syringes containing each drug were prepared by an anesthesiologist who was blinded to the study. A resident of anesthesiology blinded to the group and drug allocation applied the concealed syringes and recorded all data. IVRA was administered with 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 ml in the control group (Group LS, n=25) or with 200, 300, 400 µg NTG plus 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 ml in the NTG groups (Groups LN1, LN2, LN3, respectively; n=25 in each group). The solution was administered over 90 seconds (s) by an anesthesiologist blinded to the group assignments.

The sensory block was assessed continuously at 30 s intervals by a pinprick performed with a 22 gauge short beveled needle. Motor function was evaluated by asking the patient to flex and extend his/her wrist and fingers, and complete motor block was noted when voluntary movement was impossible. Onset of sensory block (defined as the time elapsed from injection of the study drug to sensory block achieved in all dermatomes) and onset of motor block (defined as the time elapsed from injection of the study drug to complete motor block) were recorded.

After completion of sensory and motor block, the distal cuff was inflated to 250 mmHg, and the proximal tourniquet was released. Then, the operation was started. MAP, HR, SpO_2, visual analogue scale (VAS) scores (0 = no pain and 10 = worst pain imaginable), and degree of sedation (scale 1-5, 1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, 5 = asleep and not responsive to any stimulus)[6] were recorded before and after tourniquet inflation at 1, 5, 10, 20, and 30 min after the injection of study drugs and at 1, 3, 5, 10, 15, and 30 min after tourniquet release.

Hypotension (30% decrease from baseline value) was treated with IV ephedrine (5- to 10-mg bolus), bradycardia (30% decrease from baseline value) was treated with IV atropine 0.5 mg, and arterial oxygen saturation less than 90% was treated with O_2 supplementation via a face mask.

During the intraoperative period, boluses of fentanyl 1 µg/kg were administered for tourniquet pain treatment when VAS was more than 3 and total fentanyl consumption was recorded. The time elapsed after tourniquet inflation to the first patient request for fentanyl was also recorded. Tourniquet duration was defined as time from initial proximal tourniquet inflation until deflation of the distal tourniquet at the end of the operation.

Data were recorded postoperatively at 2, 4, 8, 12, and 24 hours (h). Postoperatively, when VAS was more

than 3, 75 mg of suppository diclofenac were administered and total diclofenac consumption was recorded. The time elapsed after tourniquet release to the first patient request for diclofenac was also recorded. All assessments were performed by an anesthesia resident blinded to the study.

After the operation, qualification of the operative condition such as disturbing movement of the arm and excessive bleeding was done by the surgeon, who was unaware of the group allocation, according to the following numeric scale: 0 = unsuccessful, 1 = poor, 2 = acceptable, and 3 = perfect.

In addition, in the postoperative period, the patients were asked to qualify the operative conditions according to following numeric scale: 4 (excellent) = no complaint from patient, 3 (good) = minor complaint with no need for supplemental analgesics, 2 (moderate) = complaint that required supplemental analgesics, and 1 (unsuccessful) = patient given general anesthesia.[7]

Sensory recovery time (defined as the time elapsed after tourniquet deflation up to recovery of pain in all dermatomes determined by pinprick test) was recorded. Motor block recovery time (defined as the time elapsed after tourniquet deflation up to movement of fingers) was also recorded.

Throughout the study period, the patients were asked about any side effects (tinnitus, skin rash, gastric discomfort, vertigo, headache, nausea, and other side effects). Measurements and data recording in all patients were performed by the same person.

The statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) 15 statistical software package. Based on Sen et al.'s study,[5] a sample size of 25 in each group will have 80% power to detect a difference in the mean amount of intraoperative fentanyl requirement of 17.9 μg using a two-group t-test with a 0.050 two-sided significance level.

Statistical comparisons for quantitative data were performed using two-way ANOVA, followed by unpaired t-tests with Bonferroni correction. Nominal or categorical data were analyzed and compared using the χ^2 test.

Sedation score and the quality of the anesthesia between the four groups were compared using the Kruskal-Wallis test. Values are given as number (%), mean (SD) or median (range). A value of $p<0.05$ was considered statistically significant.

RESULTS

One hundred trauma patients were enrolled in the study. No patient was excluded from the study due to technical failure. There was no significant difference between the four groups with respect to the demographic data, type of surgical procedure and duration of surgery and tourniquet time (Table 1).

There was no significant difference between the four groups in HR, MAP and SpO_2 at any time interval during surgery or in the postoperative period. As Table 2 shows, sensory and motor block onset times were significantly shorter in Groups LN1, LN2 and LN3 compared with Group LS ($p<0.05$). Sensory and motor block recovery times were also statistically prolonged in these three groups ($p<0.05$) (Table 2). Sensory and motor block onset times were significantly shorter in Group LN3 compared with Groups LN1 and LN2 ($p<0.05$). Sensory and motor block recovery times were statistically prolonged in Group LN3 when compared with Group LN1 ($p<0.05$) (Table 2).

The initial time for beginning tourniquet and postoperative pain was significantly longer in Groups LN1, LN2 and LN3 compared with Group LS ($p<0.05$) (Table 2). This variable was significantly longer in Group LN3 compared with Groups LN1 and LN2 ($p<0.05$). The to-

Table 1. Patient characteristics, type of surgery, and operation and tourniquet times according to groups

Variable	Group LN1 (n=25)	Group LN2 (n=25)	Group LN3 (n=25)	Group LS (n=25)
Age (yr)	34.6±10.4	30.4±9.2	33.2±9.8	32.6±10.6
Gender (F/M)	6/19	3/22	7/18	8/17
Weight (Kg)	68.8±5.2	68.6±9.6	69.5±4.9	67.2±5.7
ASA (I/II)	21/4	23/2	22/3	20/5
Duration of surgery (min)	67.7±4.1	70.3±5.1	69.8±5.2	68.2±5.8
Tourniquet time (min)	74.2±5.6	78.0±5.4	76.6±5.3	75.7±6.1
Types of surgery (n)				
Carpal tunnel syndrome	5	7	4	4
Trigger finger	6	5	6	9
Tendon release	14	13	15	12

Values are presented as number or mean±SD. Group LN1 = Lidocaine-nitroglycerin 200μ group; Group LN2 = Lidocaine-nitroglycerin 300 μ group; Group LN3 = Lidocaine-nitroglycerin 400μ group; Group LS = Lidocaine-saline group. There were no significant differences between the four groups.

Table 2. Onset and recovery times of sensory and motor block, initial time of tourniquet and postoperative pain, and the amount of intraoperative and postoperative analgesic requirements according to the groups

Variable	Group LN1 (n=25)	Group LN2 (n=25)	Group LN3 (n=25)	Group LS (n=25)	p
Sensory block onset time (min)	4.1±0.9	3.5±0.8	2.8±0.6†	5.0±1.2*	0.000
Sensory block recovery time (min)	6.6±0.7	7.9±0.9	8.4±0.8‡	3.3±0.5*	0.000
Motor block onset time (min)	5.4±0.7	4.8±0.6	3.8±0.7†	6.2±0.8*	0.000
Motor block recovery time (min)	6.4±0.7	7.8±1.1	8.4±1.0‡	3.7±0.7*	0.000
The first time of tourniquet pain (min)	23.5 ±11.1	30.6±8.2	53.7±6.3†	12.6±4.5*	0.000
Intraoperative fentanyl requirement (μg)	57.9 ±14.2	32.2±12.2	25.0±0.0‡	75.0±26.3*	0.000
The first time of postoperative pain (min)	261.9±49.7	331.0± 87.9	461.7 ±147.0†	134.8±18.9*	0.000
Postoperative diclofenac requirement (mg)	75.0±0.0	75.0±0.0	75.0± 0.0	120.2±39.2*	0.000

Values are presented as mean±SD. Group LN1 = Lidocaine-nitroglycerin 200μ group; Group LN2 = Lidocaine-nitroglycerin 300μ group; Group LN3 = Lidocaine-nitroglycerin 400μ group; Group LS = Lidocaine-saline group.* p<0.05 vs. Groups LN1, LN2, LN3; † p<0.05 vs. Group LN1, LN2; ‡ p<0.05 vs. Group LN1.

tal dosage of fentanyl administration for relieving tourniquet pain was significantly less in Groups LN1, LN2 and LN3 compared with Group LS (p<0.05) (Table 2). This variable was significantly less in Group LN3 when compared with Group LN1 (p<0.05).

The median (range) sedation values at any intraoperative and postoperative period were not statistically different between the four groups. VAS scores for tourniquet pain were significantly lower at 5, 10, 20, and 30 min after tourniquet inflation in Groups LN1, LN2 and LN3 compared with Group LS during the intraoperative period (p<0.05) (Fig. 1). This variable was significantly less in Group LN3 when compared with Group LN1 at 5, 10, 20, and 30 min (p<0.05) (Fig. 1).

The total dosage of diclofenac administration for relieving postoperative pain was significantly less in Groups LN1, LN2 and LN3 compared with Group LS (p<0.05) (Table 2). Postoperative VAS scores were significantly lower at 1, 3, 5, 10, 15, and 30 min after tourniquet deflation in Groups LN1, LN2 and LN3 compared with Group LS (p<0.05) (Fig. 2). This variable was significantly less in Group LN3 when compared with Group LN1 at all the above-mentioned times (p<0.05) (Fig. 2). Postoperative VAS scores were significantly lower at 2, 4, 8, 12, and 24 h after tourniquet release in Group LN3 compared with Group LS (p<0.05) (Fig. 3). This variable was significantly less in Group LN3 when compared with Group LN1 at all the above-mentioned times (p<0.05) (Fig. 3).

In Group LN2, postoperative VAS scores were significantly lower at 2, 4, 8, and 12 h after tourniquet release when compared with Group LS (p<0.05) (Fig. 3). Postoperative VAS scores in Group LN3 were significantly lower at 12 and 24 h after tourniquet deflation when compared with Group LN2 (p<0.05) (Fig. 3).

Anesthesia quality as assessed by the patient and the surgeon was significantly better in Groups LN1,

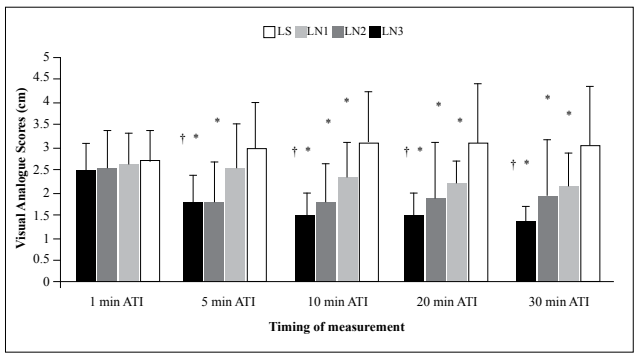

Fig. 1. Intraoperative (tourniquet pain) visual analogue scale scores. Data are presented as mean (SD). Group LN1 = lidocaine-nitroglycerin 200μ group; Group LN2 = lidocaine-nitroglycerin 300μ group; Group LN3 = lidocaine-nitroglycerin 400μ group; Group LS = lidocaine-saline group. ATI = after tourniquet inflation. * p<0.05 vs. group LS; † p<0.05 vs. group LN1.

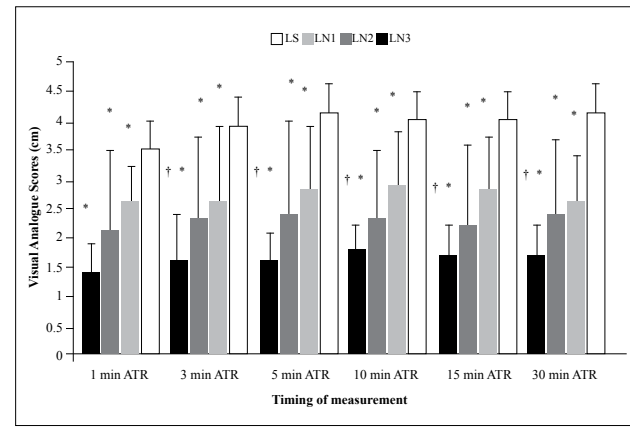

Fig. 2. Postoperative visual analogue scale scores at 1, 3, 5, 10, 15, and 30 minutes after tourniquet release. Data are presented as mean (SD). Group LN1 = Lidocaine-nitroglycerin 200μ group; Group LN2 = Lidocaine-nitroglycerin 300μ group; Group LN3 = Lidocaine-nitroglycerin 400μ group; Group LS = Lidocaine-saline group. ATR: After tourniquet release. * p<0.05 vs. Group LS; † p<0.05 vs. Group LN1.

Table 3. Quality of anesthesia as evaluated by patients and surgeon

Variable	Group LN1 (n=25)	Group LN2 (n=25)	Group LN3 (n=25)	Group LS (n=25)	p
Quality of anesthesia (Patient)	3 (2-4) *	3 (2-4) *	4 (3-4) *†	2 (2-3)	0.000
Quality of anesthesia (Surgeon)	3 (2-4) *	3 (2-4) *	4 (3-4) *†	2 (2-3)	0.000

Values are presented as median (range). * p<0.05 vs. Group LS; † p<0.05 vs. Group LN1 and Group LN2.

LN2 and LN3 compared with Group LS (p<0.05) (Table 3). This variable was significantly better in Group LN3 when compared with Groups LN1 and LN2 (p<0.05) (Table 3).

The incidence [number (%)] of hypotension was not significantly different among the four groups [3(12), 3(12), 1(4), 0(0) in Groups LN4, LN3, LN2 and LN1, respectively, p>0.05]. The incidences of tachycardia [0(0), 1(4), 1(4), 0(0)], hypertension [0(0), 0(0), 0(0), 2(8)], vertigo [2(8), 1(4), 0(0), 0(0)], headache [0(0), 0(0), 0(0), 1(4)], and nausea [2(8), 0(0), 0(0), 0(0)] in Groups LN4, LN3, LN2 and LN1, respectively, were not significantly different between the four groups (p>0.05 for all).

DISCUSSION

Providing satisfactory and prolonged analgesia is an important goal in the management of postoperative pain in trauma patients. IVRA is a technique that is mostly used for providing anesthesia and analgesia during the operation. Using additives with lidocaine may prolong the duration of postoperative analgesia.

Our study showed that the addition of 400 µg NTG to lidocaine for IVRA in trauma patients improved the speed of onset and the quality of anesthesia and decreased tourniquet pain and intraoperative and postoperative analgesic consumption better than the addition of the other two doses of NTG (200 µg or 300 µg), while causing no significant side effects.

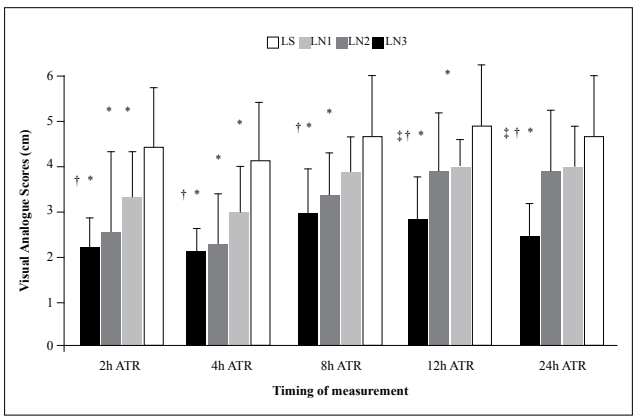

Fig. 3. Postoperative visual analogue scale scores at 2, 4, 8, 12, and 24 hours after tourniquet release. Data are presented as mean (SD). Group LN1 = Lidocaine-nitroglycerin 200µ group; Group LN2 = Lidocaine-nitroglycerin 300µ group; Group LN3 = Lidocaine-nitroglycerin 400µ group; Group LS = Lidocaine-saline group. ATR: After tourniquet release. * p<0.05 vs. Group LS; † p<0.05 vs. Group LN1. ‡ p<0.05 vs. Group LN2.

The first study on adding NTG to IVRA for hand and forearm surgery was performed by Sen and colleagues.[5] They reported that postoperative VAS scores were significantly lower for the first 4 h postoperatively in Group NTG, in which 200 µg NTG was added to IVRA. The limitation of their study was using only one low dose of NTG (200 µg). The duration of effect of NTG with this dosage was also short (4 h). They recommended further study with the other dosages of NTG. Our study showed that increasing the dosage of NTG to 400 µg significantly decreased postoperative VAS scores for 24 h after tourniquet release.

There are a variety of proposed sites for action of IVRA. Raj et al.[6] showed that the action of LA is on major nerve trunks, probably reaching the nerve trunk through small venules within the nerve core, while Rosenberg[7] provided strong evidence regarding a peripheral site. It is currently accepted that both the nerve endings and trunks are affected.[8]

The favorable effects of NTG, which we confirmed in the present study, might be influenced by a direct potent vasodilatory effect that promotes distribution of lidocaine to nerves,[9] and it seems it was dose-dependent. This would explain the more rapid onset of sensory and motor block that was seen in Group LN3.

Nitroglycerine (NTG) is metabolized to nitric oxide (NO) in the cell.[10] NO synthesis was first discovered in vascular endothelial cells,[11] central and peripheral nerve cells and fibers,[12] and macrophages.[13] NO causes an increase in the intracellular concentration of cyclic guanosine monophosphate, which generates pain modulation in the central and peripheral nervous system.[9]

Activation of the NO-cyclic guanosine monophosphate signal transduction system causes sensitization of wide-dynamic-range neurons located in the superficial and deep dorsal horns and concurrently attenuates the inhibition of the same neurons produced by stimulation in the periaqueductal gray, resulting in the transmission of painful stimuli.[14]

Nozaki et al.'s[15] study showed that peripherally applied NO donors have no analgesic effects themselves but augment the analgesic effects of peripherally administered analgesics during inflammation. This would explain the lower VAS scores and analgesic administration in groups receiving NTG, which also seems dose-dependent. In addition, NO generators induce antiinflammatory effects and analgesia by blocking hyperalgesia and the neurogenic component of inflammatory edema with topical application.[16,17]

An additional possible mechanism includes an analgesic effect through the direct stimulation of peripheral fibers imitating the actions of locally applied acetylcholine.[18] Ultimately, molecular pharmacology modulation may be suggested for the mechanism of synergistic interaction between μ-opioid receptors and NO.[19] NO has also been described to have direct modulatory effects on N-methyl-D-aspartate receptors [20] and gamma-aminobutyric acid-A receptors.[21]

The mechanisms discussed above, or their combinations, possibly contribute to the analgesic effects of NTG added to lidocaine in IVRA.

The clinical efficiency of transdermal NTG for acute pain relief has been demonstrated in several previous studies.[22,23] NTG was found to be beneficial in the treatment of shoulder pain,[24] chronic thoracotomy pain[25] and thrombophlebitis[26] and for augmenting the effect of spinal sufentanil or neostigmine,[27] or epidural S(+)-ketamine.[28] In these investigations, the analgesic effects of transdermal NTG were investigated, while in our study, the efficiency of IV NTG was documented with the mechanism similar to that of transdermal NTG.

While a variety of adjuvants have been proposed for improving intraoperative and postoperative analgesia and maintaining better operative conditions, these adjuvants may possibly cause complications such as nausea, vomiting, sedation, dizziness, wound hematoma, skin rash, and hypotension.[1-4,29] NTG may possibly cause dose-dependent side effects such as hypotension, tachycardia or headache as well.[27] In the present study, there was no significant difference in side effects between groups.

Nitroglycerine (NTG) has a very short half-life.[10] These techniques, combined with the short half-life of NTG, may diminish the incidence and severity of unwanted side effects.

In conclusion, the addition of 400 μg NTG to lidocaine in IVRA in trauma patients shortened sensory and motor block onset times, prolonged sensory and motor block recovery times, and improved tourniquet pain, while prolonging the time for the first analgesic requirement, decreasing the total amount of analgesic, and enhancing patient satisfaction better than the addition of 200 μg or 300 μg NTG, without side effects. Our study showed that the analgesic effect of NTG was dose-dependent. This point needs further investigation before a final conclusion can be elicited.

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