ORIGINAL RESEARCH / KLİNİK ÇALIŞMA

METAMIZOLE (DIPYRONE) AS AN ADDITIVE TO LIDOCAINE FOR INTRAVENOUS REGIONAL ANESTHESIA

İNTRAVENÖZ REJYONAL ANESTEZİDE LİDOKAİNE EKLENEN METAMİZOL (DİPİRON)

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SUMMARY

Background: *Nonsteroidal anti-inflammatory drugs (NSAIDs) as adjuncts to Intravenous regional anesthesia (IVRA) demonstrated analgesic effect lasting longer than the same parenteral dose. Metamizole is a potent NSAID which demonstrates peripheral analgesic properties as well. However, metamizole has not been previously studied as an additive for IVRA. We therefore tested the hypothesis that addition of metamizole to IVRA solution will decrease pain scores and improve the quality of the block.*

Material and Method: *Seventy five patients undergoing hand surgery were randomly divided into three groups. Similar IVRA solution (lidocaine 3 mg kg^{-1} diluted with saline to a total volume of 40 ml) was given to all groups. Group L received IVRA solution plus IV saline, Group L/M received IVRA solution and metamizole (500 mg) admixture plus iv saline, and Group ivM received IVRA solution plus iv metamizole (500 mg). Sensory and motor block onset time, tourniquet pain, and analgesic use were assessed during the operation. After tourniquet deflation, pain scores, time to first analgesic requirement, total analgesic consumption in 24 h, and side effects were noted.*

Results: *Pain scores after inflation of tourniquet and postoperative 1 hr was significantly lower in group ivM compared to other groups ($p<0.05$). In all other measurement times including the postoperative period there was no difference between the groups ($p>0.05$). Intraoperative fentanyl consumption and postoperative total amount of diclofenac use were similar between groups ($p>0.05$). There were no statistical differences in onset and recovery of sensory plus motor blocks between the groups ($p>0.05$). The quality of anesthesia reported by the anesthesiologist, surgeon and patient were similar between the groups ($p>0.05$).*

Conclusions: *The addition of metamizole to IVRA solution did not provide clinically significant improvement in pain scores and quality of the block.*

KEY WORDS: *IVRA; Metamizole; Lidocaine; Postoperative pain.*

ÖZET

Amaç: *Nonsteroid antiinflamatuvar ilaçlar (NSAİİ) intravenöz rejyonal anesteziye (İVRA) eklendiğinde analjezik etki süresinin aynı dozda parenteral kullanımına göre daha uzun olduğu gösterilmiştir. Potent bir NSAİİ olan metamizolün aynı zamanda periferal analjezik etkilere de sahip olduğu gösterilmiştir. Ancak metamizol daha önce İVRA'ya eklenerek çalışılmamıştır. Bu amaçla biz İVRA'ya metamizol ekleyerek ağrı skorunu düşüreceğimiz ve blok kalitesini arttırabileceğimiz hipotezini test ettik.*

Gereç ve Yöntem: *El cerrahisi geçirecek 75 hasta randomize olarak üç gruba ayrıldı. Tüm gruplara benzer İVRA solüsyonu (Toplam 40 ml serum fizyolojikle sulandırılmış Lidokain 3 mg kg^{-1}) verildi. Grup L'de İVRA solüsyonu ve iv serum fizyolojik verildi. Grup L/M'de İVRA solüsyonuna 500 mg metamizol karıştırılarak verildi. Grup ivM'de İVRA solüsyonuna ek olarak İV 500 mg metamizol ayrı olarak verildi. İlk 24 saatte duyusal ve motor blok zamanları, turnike ağrısı ve ameliyat sırasında analjezik kullanımı kaydedildi. Turnikenin indirilmesinden sonra ağrı skorları, ilk analjezik gereksinimi, 24 saatteki toplam analjezik tüketimi ve yan etkiler kaydedildi.*

Bulgular: *Turnikenin şişirilmesinden sonra ve postoperatif birinci saatte grup ivM'de diğer gruplarla karşılaştırıldığında ağrı skorları anlamlı düzeyde düşük bulundu ($p<0,05$). Postoperatif diğer tüm ölçümlerde gruplar arasında bir fark bulunamadı ($p>0,05$). İntraoperatif fentanil tüketimi ve postoperatif total diklofenak kullanımı gruplar arasında benzer bulundu ($p>0,05$). Motor ve duyusal blok başlangıç ve geri dönüş zamanları arasında istatistiksel olarak bir farklılık bulunamadı ($p>0,05$). Anestezi kalitesi gruplar arasında anestezist, cerrah ve hasta memnuniyeti açısından benzer bulundu ($p>0,05$).*

Sonuç: *İVRA solüsyonuna metamizol eklenmesi klinik olarak ağrı skorlarında ve blok kalitesinde anlamlı bir iyileşme sağlamamıştır.*

ANAHTAR KELIMELER: *İVRA; Metamizol; Lidokain; Postoperatif ağrı.*

BACKGROUND

Intravenous regional anesthesia (IVRA) is a fast, reliable and cost effective technique mainly used for short procedures of the extremities. However it has been limited by tourniquet pain, lack of postoperative analgesia and allowing limited duration for the procedure (1). Because of these drawbacks, use of this technique has been limited to ambulatory upper extremity procedures. Different additives to the local anesthetics have been used to attenuate these disadvantages related to the technique with some success (2-3). Nonsteroidal anti-inflammatory drugs (NSAIDs) have been found to be the most effective adjuncts to IVRA when compared with others. NSAIDs demonstrated analgesic benefit lasting longer than the same dose parenterally administrated (4).

Metamizole (dipyrone) is a very effective, non-opioid analgesic with significant antipyretic and spasmolytic effects. Although it was banned in some countries because of agranulocytosis (0.2-1.7 per million) it still is one of the most commonly used NSAIDs in many other counties (5). Action of antinociceptive effect seems to be through inhibition of prostaglandin synthesis in central nervous system and peripherally (6-7). Peripheral antinociceptive effects of metamizole have been attributed to cyclooxygenase inhibition (6) but have also been related with activation of nitric oxide-cyclic GMP-K channel pathway (8). There is also evidence suggesting that local analgesic pathways in opioid system are also activated by metamizole (9).

There is compelling evidence that metamizole has peripheral analgesic properties. However, metamizole has not been previously studied as an additive for IVRA. We therefore tested the hypothesis that addition of metamizole to IVRA solution will decrease pain scores and improve quality of the block.

MATERIAL AND METHOD

After ethics committee approval (Gulhane Medical Academy) and informed written consent, 75 American Society of Anesthesiology physical status I-II patients scheduled for elective hand surgery were included in the study. Patients having vascular disease and contraindication for tourniquet application were excluded from the study. Patients were randomized to 3 groups with 25 patients in each. According to randomization list identical syringes were prepared by an anesthesiology resident not involved in the study.

All patients were premedicated with 1-2 mg intravenous midazolam. Patients were later taken to operating room and standard monitoring for arterial blood pressure, oxygen saturation and heart rate were applied. Intravenous cannulae was placed on the dorsum of the operative hand for local anesthetic and study drug application. The arm was elevated for 3 minutes to allow passive exsanguination and was then exsanguinated with a 5" Esmarch bandage. A pneumatic tourniquet (Tourniquet 2800 ELC, UMB Medizin-tecknick GmbH, Germany) was then placed around the upper arm, and the proximal cuff was inflated to 250 mmHg. Isolation of the arm from the systemic circulation was verified by absence of the pulse and loss of the pulse oximetry tracing in the index finger. Group L (n=25) received 3 mg kg^{-1} lidocaine (10% Lidocaine, Aritmal, Biosel, Turkey) diluted with saline to a total of 40 ml, group L/M (n=25) received 3 mg kg^{-1} lidocaine plus 500 mg metamizole (Novalgin 500 mg, Sanofi-Aventis) diluted with saline to a total of 40 ml and group ivM (n=25) received 3 mg kg^{-1} lidocaine diluted with saline to a total of 40 ml for IVRA. Groups L and L/M received 2 ml of saline and group ivM received 500 mg metamizole within 2 ml of saline intravenously after injection of IVRA medication.

After study drug injection sensory and motor block was assessed by a resident blinded to group allocation. For sensory assessment 22-G needle was used and pinprick testing was performed until the start of surgery in the hand and forearm. Patients were evaluated also for motor function by asking the patient to flex and extend his/her wrist and fingers. Complete motor block was accepted when patient had no voluntary movement. Sensory block onset time was accepted as the time from injection of the study drug to complete sensory block in all dermatomes, and motor block onset time was accepted as the time from injection of study drug to patient having no voluntary movement.

Surgery was initiated after complete sensory and motor block with releasing proximal tourniquet and inflating the distal tourniquet to 250 mmHg. Hemodynamic parameters and oxygen saturation levels were recorded through the procedure by an anesthesiology resident, who was blinded to the medication administered.

Tourniquet pain was assessed with a 10 cm visual analogue scale (VAS). Levels of sedation were assessed with Ramsey sedation scale. Both VAS and sedation levels were recorded during the procedure.

Patients were assessed for pain intraoperatively, 1 µg kg^{-1} fentanyl was given if patients had pain score of VAS > 4. Intraoperative hypotension (systolic arterial blood pressure <90 mmHg or 50 mmHg lower than the baseline value) was treated with 5 mg iv ephedrine, bradycardia (HR < 50/min) was treated with 0.5 mg iv atropine. Nausea and vomiting was treated with 4 mg iv ondansetron. Oxygen was given via nasal cannulae and end tidal CO_2 was monitored. All of the complications and time of occurrence was recorded.

Quality of anesthesia related to block was evaluated by an attending anesthesiologist blinded to the study drug using the following scale: '4' excellent, no complaint related to pain from the patient; '3' good, minor complaint with requirement for supplemental analgesics; '2' moderate, significant complaint that required supplemental analgesic; '1' unsuccessful, failed block where patient had to be given general anesthesia. Assessment of surgical block was done by the surgeon blinded to allocation using the following scale: '3' perfect, '2' acceptable, '1' poor, '0' unsuccessful. Patient satisfaction related to technique was graded as follows: '4' excellent, '3' good, '2' moderate, '1' poor.

Tourniquet duration was limited to two hours and was not deflated before 30 minutes. At the end of surgery, the tourniquet deflation was performed by two-stage deflation to decrease the possibility of systemic toxicity from the local anesthetic. Sensory recovery time was accepted as the time from tourniquet deflation to recovery of pain in all nerve distributions assessed by pinprick test. Motor block recovery time was accepted as the time from tourniquet deflation to patient having voluntary movement. First analgesic requirement time was noted as the time elapsed from tourniquet release to first request of analgesic.

Patients were assessed by an anesthesiology resident blinded to group allocation for mean arterial pressure, heart rate, SpO_2, VAS, sedation and side effects at 1, 2, 4, 6, 12 and 24 hours postoperatively. Patients with pain score of VAS > 4 was treated by 75 mg im diclofenac. Analgesic consumption and time was noted by a blinded anesthesia resident.

The sample size estimation showed that 24 patients were required in each group to detect reduction at the level of pain by 35% (2.0 vs 1.3) with a power of 0.80 and level of significance of □=0.05. According to the distribution of the data; Kruskal Wallis, Mann Whitney U test, analysis of variance, and Chi-square tests were performed. Bonferroni correction was performed for repeated testing. Data were mean (SD), number (%), or median (min-max). Statistical analysis was performed with SPSS for Windows version 11.5 (SPSS Inc. Chicago, IL). A p value of <0.05 was accepted as statistically significant.

RESULTS

All groups were similar with regard to demographics, ASA, duration of surgery and duration of tourniquet (Table 1). Intra-postoperative MAP, HR or SpO_2 were similar at any measured time point (Data not presented). Types of surgical procedures were similar between all groups (Table 1). All patients were able to complete the study and there were no exclusions in data analysis.

Pain scores after inflation of tourniquet and postoperative 1 hr was significantly lower in group ivM

Table 1. Demographic Characteristics of the patients.

	Group L (n = 25)	Group L/M (n = 25)	Group ivM (n = 25)
Age (year)	39 ± 12	41 ± 17	43 ± 16
Weight (kg)	77 ± 14	72 ± 7	76 ± 15
Height (cm)	168 ± 9	170 ± 10	161 ± 21
ASA (I/II)	23/2	21/4	20/5
Sex (male/female)	15/10	17/8	13/12
Type of surgery			
(Carpal Tunnel/Tendon repair/Phalanx fracture)	14/8/3	17/6/2	15/6/4
Operation time (min)	39 ± 26	45 ± 27	35 ± 21
Tourniquet time (min)	56 ± 25	56 ± 28	50 ± 18

*Values are mean+SD. ASA: American Society of Anesthesiologists
No significant differences were found between the groups.

Table 2. Onset and Recovery Times of Sensory and Motor Block (min)

	Group L (n = 25)	Group L/M (n = 25)	Group ivM (n = 25)
Sensory block onset time (min)	4.9 ± 2.5	4.8 ± 1.9	4.1 ± 1.6
Sensory block recovery time (min)	5.0 ± 1.9	6.2 ± 3.0	6.4 ± 3.4
Motor block onset time (min)	8.8 ± 4.2	7.6 ± 2.4	8.4 ± 4.3
Motor block recovery time (min)	5.5 ± 3.8	6.2 ± 2.5	5.6 ± 3.4

*Values are mean+SD.
No significant differences were found between the groups.

Table 3. Analgesic Use and Quality of technique Determined by Anesthesiologist and Surgeon.

	Group L (n = 25)	Group L/M (n = 25)	Group ivM (n = 25)
First analgesic request time (min)	106 ± 167	122 ± 163	141 ± 156
Total amount of postoperative diclofenac (mg)	126 ± 50	115 ± 54	117 ± 55
Intraoperative fentanyl consumption(µg)	77 ± 13	79 ± 12	75 ± 11
Patient Satisfaction score	3.2 ± 0.6	3.3 ± 0.5	3.2 ± 0.7
Quality of anesthesia (anesthesiologist)	3.1 ± 0.7	3.4 ± 0.5	3.0 ± 0.9
Quality of anesthesia (surgeon)	2.7 ± 0.6	2.9 ± 0.4	2.5 ± 0.5

Values are mean+SD and median (range).
No significant differences were found between the groups.

compared to other groups ($p<0.05$). In all other measurement times including the postoperative period, there was no difference between the groups ($p>0.05$) (Figure 1). Intraoperative fentanyl consumption and postoperative total amount of diclofenac use were similar between groups ($p>0.05$) (Table 2). Sedation scores were similar between the groups in all measured times (not reported).

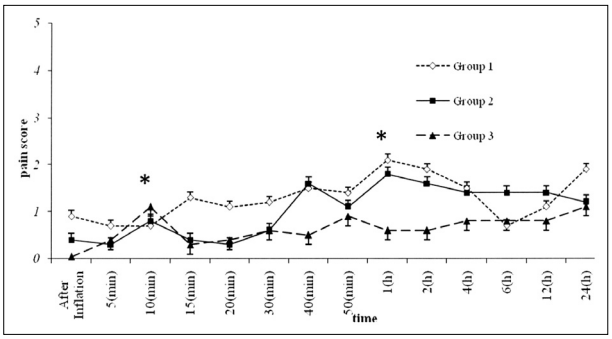

Figure 1. Intraoperative and postoperative pain scores. *p<0.05 with Bonferroni corrected Mann Whitney U (Group (3) ivM compared with Group (1) L and (2) L/M)
***p<0.05 with Bonferroni corrected Mann Whitney U (Group (3) ivM compared with Group (1) L and (2) L/M)**

There were no statistical differences in onset and duration recovery of sensory block between the groups, furthermore there were no statistical differences in onset and duration recovery of motor block ($p>0.05$) (Table 3).

The quality of anesthesia scores reported by the anesthesiologist and surgeon showed there was no difference between the groups; similarly patient satisfaction scores were similar between the groups ($p>0.05$) (Table 2).

The only postoperative side effects demonstrated was nausea in three patients in group ivM, and two patients in groups L and L/M.

DISCUSSION

Previous studies (10-13) and systemic review by Choyce et al. (4) suggest that NSAIDs are the most effective adjuncts to IVRA. From NSAIDs ketorolac was the most preferred additive used. In a number of trials, ketorolac demonstrated significant benefit in regards to pain and postoperative analgesic consumption (13-14). Recent studies with relatively newer NSAIDs were also used successfully in IVRA. Tenoxicam and lornoxicam shortened the onset of sensory and motor block, decreased tourniquet pain and improved postoperative analgesia (11,15,16). In a recent study the 'non-classical' NSAID paracetamol decreased tourniquet pain, increased anesthesia quality, and decreased postoperative analgesic consumption (10).

Surprisingly, in our current study addition of the `non-classical` NSAID metamizole to IVRA solution didn't provide clinically significant improvement in pain scores and quality of the block. Drugs to be effective as an additive in IVRA should either have direct effect on nerve conduction or have peripheral antinociceptive effects. Metamizole demonstrates significant peripheral analgesic effect by inhibition of COX enzymes (6) and also activates ATP-gated K^+ channels (17). The simplest explanation of these results is to postulate that the dose we used may have been insufficient; although in IVRA, local anesthetics and adjuvant are given in very close proximity of the surgical site and are isolated from distribution to systemic circulation as well. Another explanation may be related to metamizole being a prodrug needing to be converted nonenzymatically in the presence of oxygen to active derivatives (18). Hydrolysis of metamizole to active derivates is dependent on concentration, temperature and pH (19); which may have been effected from ischemia, hypothermia or acidity produced by tourniquet application (20).

Unlike the other NSAIDs, metamizole produces analgesic effects associated with a less potent anti-inflammatory action (21). Therefore it has been proposed that the antinociceptive effect of metamizole is mediated at least in part by central mechanisms. And this may have also contributed to our results, demonstrating some

analgesic benefit in the systemic administrated group and no clear benefit as an adjuvant to the IVRA solution. Current study provides information about clinical use of metamizole as an adjunct in IVRA; however, this may be a useful model for studying the peripheral analgesic action of metamizole in the absence of central effects as well.

An important limitation of the current study relates to the arbitrarily chosen dosage of the study drug (namely, 500 mg of metamizole). However, there is no study that has been done previously to determine the effective dose. In order to optimize the dose of metamizole, a dose ranging study design including lower doses would be required. Another limitation of this study relates to the fact that the study population involved only patients undergoing minor hand surgery procedures.

In conclusion, the addition of metamizole to lidocaine in IVRA did not provide clinically significant improvement in pain scores and quality of the block. Further studies are needed to determine postulated peripheral analgesic effect of metamizole in different clinical techniques.

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