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Original Article

Adding metoclopramide to lidocaine for intravenous regional anesthesia in trauma patients

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Abstract

Background: Metoclopromide have local anesthetic properties. The main object of performing the present study was to evaluate the analgesic effect of metoclopromide 10 mg when added to lidocaine for intravenous regional anesthesia (IVRA) of upper extremities in trauma patients.

Materials and Methods: Ninety patients undergoing upper limb producer were randomly allocated to the three groups to receive 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 ml (Group L, $n = 30$) or 10 mg metoclopromide plus 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 ml (group LM, $n = 30$) or 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 ml plus 10 mg metoclopromide intravenously (Group IM, $n = 30$).

Results: Our study showed that the onset times for sensory and motor block were significantly shorter in Group LM compared with Group L and Group IM (4.5 ± 0.7 vs. 5.0 ± 0.7 and 5.0 ± 0.6, respectively, $P = 0.006$ for sensory block; 6.3 ± 0.7 vs. 5.1 ± 0.9 and 5.9 ± 0.6 respectively, $P = 0.000$ for motor block). The postoperative VAS scores were significantly less at 1, 5, 10, 15, and 30 minutes after tourniquet release in Group LM compared with Group L and Group IM ($P < 0.05$).

Conclusion: The results of our study showed that adding 10 mg metoclopromide to lidocaine for IVRG in trauma patients reduced intraoperative and postoperative analgesic use till 24 hours and improve quality of anesthesia.

Key Words: Anesthetic techniques, intravenous regional anesthesia lidocaine, metoclopromide, postoperative pain

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INTRODUCTION

Intravenous regional anesthesia (IVRA) is a reliable, simple, and cost-effective technique of regional anesthesia in trauma patients that used for performing short surgical procedures in the extremities.[1] IVRA has some disadvantages that include slow onset of sensory and motor block, inadequate muscle relaxation, toxicity of local anesthetic (LA), tourniquet pain, and short duration of postoperative analgesia.[1-6]

Different additive such as tramadol, opioids, muscle relaxants, dexmedetomidine and nonsteroidal anti-inflammatory drugs combined with LA for improving quality of block, prolonging postoperative

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analgesia, and decreasing tourniquet pain.[1-8]

Metoclopramide is a central trigger-zone inhibition drug which has powerful antiemetic effect.[9] In addition to antiemetic effect, it was shown that metoclopromide is a weak local anesthetic in its own right.[10] The probable mechanism of analgesic effect of metoclopromide is reversible blocks of pathways for peripheral nerve stimulation by its effect on excitable membrane.[11]

Liaw and colleagues[11] investigated the efficacy of intravenous metoclopramide compared with lidocaine in decreasing pain during injection of propofol and showed that both drugs had similar efficacy for the control of pain. They showed that efficacy of metoclopromide in this regard was comparable with flurbiprofen axetil in their study.

In another study, it was reported that IV administration of metoclopromide significantly reduced pain during nasogastric tube insertion in comparison with placebo.[12] Also, the analgesic effect of metoclopromide was shown in uretheric colic.[13]

To the best of our knowledge, there was no study to evaluate the analgesic effect of metoclopromide as additive in IVRA. Therefore, we planned this study to investigate the effect of adding metoclopromide 10 mg to the lidocaine for IVRA in trauma patients on sensory and motor block onset and recovery times, intraoperative and postoperative pain, tourniquet pain, the quality of anesthesia, intraoperative and postoperative hemodynamic variables, and the adverse effects. Also, it has not been shown in the previous studies which analgesic effect of metoclopromide was a peripheral or central effect. So, the evaluation of peripheral and central effect of metoclopromide is another purpose of designing this study.

MATERIALS AND METHODS

The study was performed after obtaining institutional approval from Ethic committee of our university. Ninety trauma patients with American Society of Anesthesiologist (ASA) physical status I-II patients, aged 18-65 years old which had no Reynaud disease, sickle cell anemia or who had no history of allergy to any drug used candidate for elective hand or forearm surgery due to soft tissue injury gave written informed consent to include in this randomized prospective double-blind study. If the technique of anesthesia was changed, the patient was excluded from the study.

No premedication was given to the trauma patients. In the preoperative visit by anesthesiologist, a visual analog scale (VAS) consisting of a 10-cm line, in which 0 represented no pain and 10 represented the worst possible pain, was explained to all of patients. After arrival of patients to the operating room, mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), and heart rate (HR) were monitored.

Before beginning the block, one 18 gauge intravenous cannula was inserted in a dorsal vein of the operative hand and the other one in the opposite hand for infusion of crystalloid. At first, operating arm was exsanguinated with an Esmarch bandage. It was maintained elevated for 3 minutes. Then after, a 10 cm pneumatic padded double-tourniquet was positioned around the upper arm while proximal cuff was inflated to 250 mmHg. The circulatory isolation of the arm was confirmed if there was no radial pulse and pulse oximetry tracing in ipsilateral index finger.

After providing a randomization list, an anesthesiologist who was blinded to the study drugs prepared identical syringes. Administration of drugs and data collection was performed by another anesthesiologist who was blinded to the group allocation. The patients were randomized by a computer generated table into three groups: Group L ($n = 30$) which IVRA begun in hand injury with 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 mL and in the other hand with 2 mL normal saline intravenously; Group LM ($n = 30$) which IVRA begun in hand injury with 10 mg metoclopromide plus 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 mL and in the other hand with 2 mL normal saline intravenously; Group IM ($n = 30$) which IVRA begun in hand injury with 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 mL and in the other hand with metoclopromide 10 mg in volume of 2 ml intravenously.

By using a 22 gauge short beveled needle, we continuously evaluated the sensory block continuously at 30 second intervals by a pinprick. The patients' response was evaluated in the dermatomal sensory distribution of the medial and lateral antebrachial cutaneous, ulnar, median, and radial nerves. By asking the patient to flex and extend his/her wrist and fingers, the motor function was evaluated. When voluntary movement was impossible, we considered it as complete block.

The time elapsed from injection of study drug to sensory block achieved in all dermatomes was considered as onset of sensory block which was recorded. Also, the time elapsed from injection of study drug to complete motor block was considered as onset of motor block and was recorded.

After obtaining complete sensory and motor block,

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the distal cuff was inflated to 250 mm Hg, and the proximal tourniquet was deflated. After that the surgeon was permitted to begin surgery. MAP, HR, SpO_2, VAS scores, 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)[14] were recorded before and just after tourniquet inflation, at 1, 5, 10, 15, 30 minutes after the injection of study drugs and at 1, 5, 10, 15, 30 minutes after tourniquet deflation.

During operation, the boluses of fentanyl 1 μg/kg were administered for tourniquet pain with VAS more than 3 and total dosage of fentanyl administered was recorded. The time from tourniquet inflation to the first patient request for fentanyl was also recorded. Tourniquet duration was described as time from initial proximal tourniquet inflation until deflation of the distal tourniquet at the end of operation. MAP, HR, SpO_2, VAS scores were recorded at 2, 4, 8, 12, and 24 h after operation. If patients had VAS more than 3 during postoperative periods, 75 mg of suppository diclofenac were administered and total dose diclofenac usage was recorded. The time from tourniquet deflation to the first patient request for diclofenac was also recorded.

Qualification of surgical condition such as disturbing movement of the arm and too much bleeding (scale: 0 = unsuccessful, 1 = poor, 2 = acceptable, and 3 = perfect) was evaluated by the surgeon who was not informed from study group. Also, qualification of the operative conditions [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 at postoperative period][15] was evaluated by the anesthesiologist who was blinded to the group allocation. Deflation of tourniquet did not perform before 30 minutes and it was not inflated for more than 1.5 hours. The tourniquet deflation was done by cyclic deflation technique at the end of operation.

The time from tourniquet deflation up to recovery of pain in all dermatomes as determined by pinprick test was defined as sensory recovery time which was recorded. Also, the time from tourniquet deflation up to movement of fingers was defined as motor block recovery time and was recorded. Side effects including tinnitus, skin rash, gastric discomfort, vertigo, headache and nausea were also recorded in trauma patients.

The data of study were analyzed by using the Statistical Package for Social Sciences (SPSS) for Windows, version 16.0. A sample size of 30 patients per group was estimated to provide 80% power to detect a difference in means amount of intraoperative fentanyl requirement of 17.9 μg assuming that standard deviation (SD) in Group L and Group LM was 13.3 and 25.6, respectively using a 0.050 two-sided significance level. Two-way ANOVA, followed by unpaired *t*-tests with Bonferroni's correction was used for analysis of demographic data, intraoperative, postoperative hemodynamic data, the time of the onset and the recovery of the sensory block, and motor block, the duration of the operation and tourniquet, the onset time of tourniquet pain, and intraoperative-postoperative analgesic us among the three groups. The Chi-square test was used for analysis of nominal or categorical data between three groups. By using the Kruskal–Wallis test, sedation scores and the quality of the anesthesia between the three groups were compared. Values are presented as number (%), mean (SD), or median (range). P <0.05 was considered significant statistically.

RESULTS

Ninety trauma patients were included in the study. We had no patient who excluded from the study due to any problem. There was no significant difference between three groups with respect to the demographic data, duration of surgery and tourniquet pain [Table 1]. All surgeries were tendon repair due to soft tissue injury.

There were no significant differences between three groups in heart rate, mean arterial pressure and SpO_2 recorded at different time intervals ($P > 0.05$). The onset times for sensory and motor block were significantly shorter in Group LM compared with Group L and Group IM ($P < 0.05$) [Table 2]. The recovery times for sensory and motor block were significantly longer in Group LM and Group IM compared with Group L ($P < 0.05$) [Table 2]. There was no significant difference between Group LM with Group IM in this regards ($P > 0.05$) [Table 2].

Table 1: Patients' demographic data, duration of operation and tourniquet inflation in three groups

Variable	Group L (*n*=30)	Group LM (*n*=30)	Group IM (*n*=30)
Age (yr)	33.4±10.0	30.2±7.1	32.4±8.5
Gender (F/M)	4/26	5/25	3/27
Weight (kg)	69.7±10.5	71.9±9.8	68.4±8.1
ASA (I/II)	25/5	23/7	24/6
Duration of surgery (min)	65.3±7.4	64.8±8.5	63.5±7.9
Tourniquet time (min)	76.3±6.3	75.7±7.6	73.5±7.8

Values are presented as mean±SD or number. Group L: Lidocaine group; Group LM: Lidocaine-metoclopromide group; Group IO: Intravenous metoclopromide group. No significant difference was noted among three groups

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Table 2: Onset and recovery times of sensory and motor block, initial time of tourniquet and postoperative pain, and total amount of intraoperative and postoperative analgesic use in three groups

Variable	Group L (*n*=30)	Group LM (*n*=30)	Group IM (*n*=30)	*P* value
Sensory block onset time (min)	5.0±0.7	4.5±0.7*†	5.0±0.6	0.006
Sensory block recovery time (min)	5.1±0.9†	6.3±0.7*	5.9±0.6	0.000
Motor block onset time (min)	5.5±0.8	4.9±0.7*†	5.4±0.6	0.006
Motor block recovery time (min)	4.6±0.8†	5.8±0.8*	5.4±0.6	0.000
The first time of tourniquet pain (min)	9.3±2.5	39.3±10.4*†	13.7±5.8	0.000
Intraoperative fentanyl requirement (μg)	65.2±10.8	21.4±10.7*†	64.4±8.8	0.000
The first time of postoperative pain (min)	69.2±24.2†	114.0±26.7*	127.5±34.1	0.000
Postoperative diclofenac requirement (mg)	83.6±38.7†	47.5±7.9*	53.7±10.6	0.006

Values are presented as mean±SD. Group L: Lidocaine group; Group LM: Lidocaine-metoclopram ide group; Group IM: Intravenous metoclopromide group. * *P*<0.05 vs. Group L; †*P*<0.05 vs. Group IM

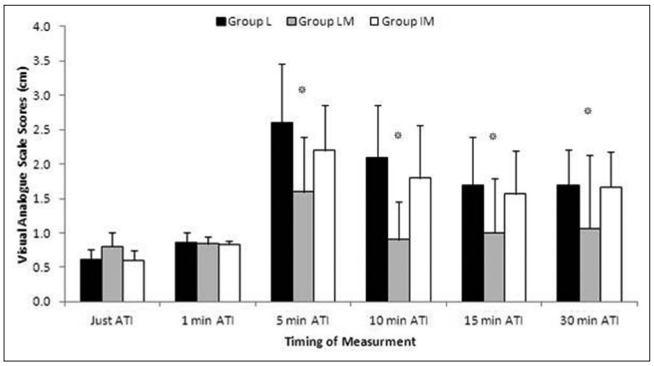

Figure 1: Intraoperative (tourniquet pain) visual analogue scale scores. Data are presented as mean±SD. Group L=Lidocaine group; Group LM=Lidocaine-metoclopromide group; Group IM=Intravenous metoclopromide group. ATI=After tourniquet inflation. *$P < 0.05$ vs. Group L and Group IM

There was no significant difference among three groups in median sedation level at any intra-operative and postoperative period. The VAS scores for tourniquet pain during the intra-operative period were significantly less in Group LM compared with Group L and Group IM at 5, 10, 15, and 30 minutes after tourniquet inflation ($P < 0.05$) [Figure 1]. No significant difference was noted between Group L with Group IM in this regards.

The first time for initiation of tourniquet pain was significantly longer in Group LM compared with Group L and Group IM ($P < 0.05$) [Table 2]. The total dosage of fentanyl used for relieving tourniquet pain was significantly less in Group LM compared with Group L and Group IM ($P < 0.05$) [Table 2]. There was no significant difference between Group L with Group IM in this regards. The postoperative VAS scores were significantly less in Group LM compared with Group L and Group IM at 1, 5, 10, 15, and 30 minutes after tourniquet release ($P < 0.05$) [Figure 2]. This variable was significantly less in Group IM compared with Group L at 30 minutes after tourniquet release ($P < 0.05$) [Figure 2].

Also, postoperative VAS scores were significantly less in Group LM and Group IM compared with Group L at 2, 4, 8, 12, and 24 hours after tourniquet deflation ($P < 0.05$) [Figure 3]. No significant difference was noted between Group LM with Group IM in this regards. The first time for rescue analgesic was significantly longer in Group LM and Group IM compared with Group L ($P < 0.05$) [Table 2]. No significant difference was noted between Group LM with Group IMN in this regards.

The total dosage of analgesic used for relieving postoperative pain was significantly less in Group LM and Group IM compared with Group L ($P < 0.05$) [Table 2]. No significant difference was noted between Group LM with Group IMN in this regards.

Quality of anesthesia which evaluated by the patients and the surgeon was significantly more in Group LM and Group IM compared with Group L ($P < 0.05$) [Table 3]. There was no significant difference between Group LM with Group IM in this regards. There was no significant adverse effect in any patient during the study period.

DISCUSSION

The results of the present study showed that addition of metoclopromide 10 mg to lidocaine for IVRG in trauma patients significantly improved the onset time and duration of sensory and motor block, decreased tourniquet pain, decreased intraoperative and postoperative analgesic use till 24 hours compared with Group L without causing important adverse effects.

Also, our data showed that administration of intravenous metoclopromide 10 mg in trauma patients significantly prolonged duration of sensory and motor block, decreased the first time for rescue analgesic and postoperative analgesic requirements till 24 hours compared with Group L. The quality of anesthesia was also significantly better in Group LM and Group IM compared with Group L.

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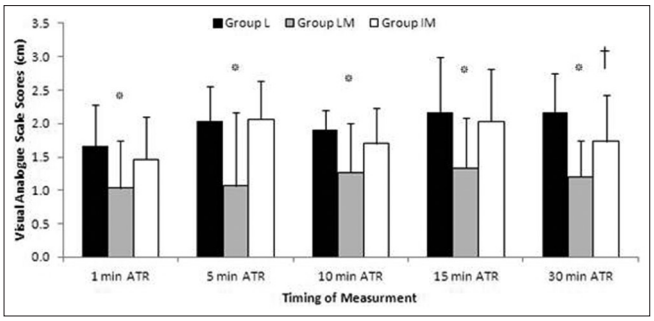

Figure 2: Postoperative visual analogue scale scores at 1, 5, 10, 15, and 30 minutes after tourniquet release. Data are presented as mean ± SD. Group L=Lidocaine group; Group LM=Lidocaine-metoclopromide group; Group IM=Intravenous metoclopromide group. ATR=After tourniquet release. **P* < 0.05 vs. Group L and Group IM. †*P* < 0.05 vs. Group L

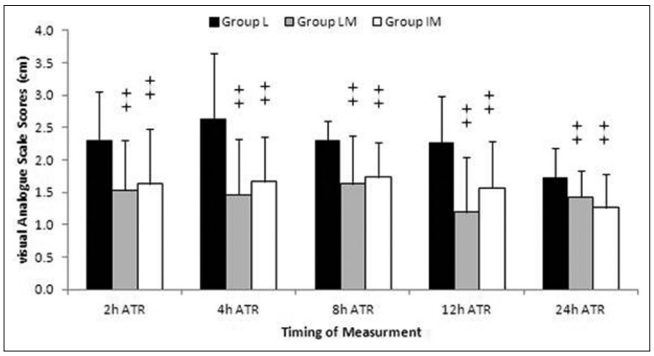

Figure 3: Postoperative visual analogue scale scores at 2, 4, 8, 12, and 24 hours after tourniquet release. Data are presented as mean±SD. Group L=Lidocaine group; Group LM=Lidocaine-metoclopromide group; Group IM=Intravenous metoclopromide group. ATR=After tourniquet release. †*P* < 0.05 vs. Group L

Table 3: Quality of anesthesia which evaluated by patients and surgeon

Variable	Group L (*n*=30)	Group LM (*n*=30)	Group IM (*n*=30)	*P* value
Quality of anaesthesia (Patient)	2 (1-4)	3 (1-4)*	3 (1-4)†	0.000
Quality of anaesthesia (Surgeon)	2 (1-4)	3 (1-4)*	3 (1-4)†	0.000

Values are presented as median (range). Group L: lidocaine group; Group LM: lidocaine-metoclopromide group; Group IM: Intravenous metoclopromide group *P<0.05 vs. Group L. †P<0.05 vs. Group L

In a study that was performed by fujii and colleagues[14] it was shown that administration of intravenous metoclopromide 10 mg, preceded by venous occlusion for 2 minutes, significantly reduced pain during injection of propofol. Metoclopromide has structural and physicochemical properties similar to lidocaine, procaine,[11] and procainamide[11] and is a local anesthetic in its own right. The probable mechanism by which metoclopromide decreased pain accompanied with propofol is reversible blocks of peripheral nerve pathways through the action on excitable membranes in the arms.[16] Also, it was shown that metoclopromide alter the influx of calcium ions across the membrane to produce a generalized analgesic effect.[17]

In a clinical trial study which designed by Liaw *et al.*[11] it was concluded that intravenous retention of metoclopromide with use of tourniquet was the most effective method for decreasing pain after injection of propofol. The efficacy of metoclopromide in reducing pain during injection of propofol was comparable with lidocaine and flurbiprofen axetil in that study. Ozucelik *et al.*[17] showed that mean VAS levels of nausea, discomfort and pain during nasogastric tube insertion were significantly lower following administration of IV metoclopromide 10 mg as compared with placebo. Although they did not use a systemic or local medication for pain relieving, there was a significant reduction in pain. It is probable that pain, nausea, and discomfort work together synergistically. Therefore patients with reduced nausea and discomfort feel less pain. Moreover, it was presumed that with decrease in nausea and discomfort during NGT insertion, additional physical movements were reduced in the patients and consequently decreased the physical origin of pain produced by insertion of NGT.

Fujii and *et al.* colleagues[18] showed that a pretreatment with lidocaine 20 mg iv or lidocaine 20 mg in combination with metoclopromide 10 mg iv with venous occlusion for one minute was effective in reducing pain on injection of propofol. In their study, lidocaine-metoclopromide combination was more effective than using lidocaine alone for decreasing such pain. In a study that was performed by Ceyhan *et al.*[19] metoclopromide was compared with tramadol for prevention of postoperative pain. They concluded that metoclopromide was significantly effective for prevention of postoperative pain and can be use as an alternative to tramadol. They recommended using metoclopromide in combination with the other analgesics because it will decrease the analgesic dosage and adverse effects, thus making it as a agent of choice.

Metoclopromide which acts as an antagonist of dopamine is a central cholinergic and agonist. It was shown that the analgesic effect of metoclopromide is due to increase in prolactin (PRL) secretion.[20] Kandler *et al.*[20] showed that the analgesic effect of metoclopromide was due to reaction between PRL and endogenous opioids system while in the same time it prevented nausea and vomiting without had significant adverse effects.

Hendenbro and *et al.* colleagues[21] evaluated the analgesic effect of the narcotic agent combination of metilscopolamine–papaverin, HCl–morphine, HCl–noscapine, HCl–codeine, and HCl with metoclopromide in forty patients with uretheric

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colic. They showed that both agents had similar analgesic effects. They reported that metoclopromide has cholinomimetic and prokinetic effects and recommended its usage in treatment of urethral colic especially where nausea is present and using the other methods of therapy is prohibited. The analgesic effect of metoclopramide in the genitourinary tract may be due to its antagonism of the dopamine receptors, as well as its cholinergic activity, which decreases smooth muscle spasm and increases effective peristaltic action.[22]

Kandler and Lisander[20] evaluated the postoperative analgesic effect of metoclopromide in patients underwent total hip prosthesis under spinal anesthesia and showed that the pain-free intervals was longer in patients received metoclopromide and total dose of morphine used was less. Ramaswamy *et al.*[23] evaluated the analgesic effects of metoclopromide via the chemical route in rats and showed that metoclopromide has analgesic effect by increasing PRL secretion.

Ganta and colleagues[16] investigated the effect of lidocaine and metoclopromide in decreasing pain associated with propofol injection and showed that both drugs lowered severity of pain distinctly in comparison with control group. Vella *et al.*[24] showed that metoclopromide increased analgesia produced by pethidine and decreased rescue analgesic in pregnant patients while had no change in Apgar score of the babies. Lin and colleagues[25] emphasized the advantage of metoclopromide that in addition to eliminating nausea and vomiting, they also produce analgesic effect.

Colman *et al.*[26] showed that in patients with acute migraine, metoclopromide reduced headache pain more than control group. Majedi *et al.*[27] showed that pretreatment with metoclopromide 10 mg was effective in decreasing pain during injection of diazepam. In a study that was performed by Mecklem[28] it was shown that incidence of pain during injection of propofol was similar in group received metoclopramide-propofol mixture with group received lidocaine-propofol combination.

Ganta *et al.*[16] showed that i.v. metoclopromide significantly decreased morphine requirements in patients underwent second trimester abortion. Also, it was reported that i.v metoclopromide decreased spasm in the fallopian tube which may be on this basis that venous pain is attenuated.[18,24,28] The dystonia and extrapyramidal side effects of metoclopromide was reported in dose more than 20 mg. The dose of metoclopromide in our study was 10 mg and we had no such adverse effects.

In contrast to the results of our study, in a randomized, double blind, placebo controlled clinical trial which performed in patients undergoing cesarean delivery and received 10 mg intravenous metoclopromide before spinal anesthesia, Danzer *et al.*[29] reported that metoclopromide decrease nausea perioperatively but does not decrease postoperative morphine needs by clinically significant amount. Their explanation for absence of analgesic effect of metoclopromide in comparison with the other studies was inadequate blood level of metoclopromide which was needed for analgesic effect and/or type of surgery.

In conclusion, our study showed that adding metoclopromide 10 mg to lidocaine for IVRA in trauma patients reduced intraoperative and postoperative analgesic use till 24 hours, decreased onset of sensory and motor block, increased duration of sensory and motor block, decreased tourniquet induced pain, prolonged the rescue time for analgesic use, and finally improved the patients' and surgeons' satisfaction without causing significant adverse effects. Also, our findings revealed that administration of metoclopromide 10 mg intravenously can improve quality of postoperative analgesia. Our data showed that metoclopromide has both local and central analgesic effects. As our knowledge showed, this is the first study which evaluated the effect of metoclopromide when added to IVRA. The authors believe that more studies must be performed before final conclusion can be elucidated.

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