Rev Bras Anestesiol. 2013;63(4):311-316

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br

SCIENTIFIC ARTICLE

Comparison of Lornoxicam and Fentanyl when added to Lidocaine in Intravenous Regional Anesthesia

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Received from Ege University, School of Medicine, Department of Anesthesiology and Reanimation, Izmir, Turkey.

Submitted on April 24, 2012. Approved on July 30, 2012.

Keywords:
Anesthesia, Conduction;
Anesthetics, Local;
Fentanyl;
Lidocaine;
Piroxicam/lornoxicam.

Abstract

Background and objectives: In this study, our goal was to compare intraoperative and postoperative analgesic effects of lornoxicam and fentanyl when added to lidocaine Intravenous Regional Anesthesia (IVRA) in a group of outpatients who underwent hand surgery.

Methods: This is a double blind randomized study. A total of 45 patients were included, randomized into three groups. Patients in Group I (L) received 3 $mg.kg^{-1}$ of 2% lidocaine 40 mL; patients in Group II (LL) received 3 $mg.kg^{-1}$ lidocaine 38 mL + 2 mL lornoxicam; patients in Group III (LF) received 3 $mg.kg^{-1}$ lidocaine 38 mL + 2 mL fentanyl. Our primary outcome was first analgesic requirement time at postoperative period.

Results: Lornoxicam added to lidocaine IVRA increased the sensory block recovery time without increasing side effects and increased first analgesic requirement time at the postoperative period when compared to lidocaine IVRA ($p < 0.001$, $p < 0.001$ respectively) and fentanyl added to lidocaine IVRA ($p < 0.001$, $p < 0.001$ respectively). In addition, we also found that fentanyl decreased tourniquet pain ($p < 0.01$) when compared to lidocaine but showed similar analgesic effect with lornoxicam ($p > 0.05$) although VAS scores related to tourniquet pain were lower in fentanyl group. Lornoxicam added to lidocaine IVRA was not superior to lidocaine IVRA in decreasing tourniquet pain.

Conclusions: Addition of fentanyl to lidocaine IVRA seems to be superior to lidocaine IVRA and lornoxicam added to lidocaine IVRA groups in decreasing tourniquet pain at the expense of increasing side effects. However, lornoxicam did not increase side effects while providing intraoperative and postoperative analgesia. Therefore, lornoxicam could be more appropriate for clinical use.

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ISSN/$ - see front metter

doi: 10.1016/j.bjane.2012.07.001

Introduction

Intravenous regional anesthesia (IVRA) is a safe and fair efficient method that is easy to perform in outpatient extremity surgery lasting less than one hour [1]. The success rate of IVRA is approximately 95-100%. The advantage of this method is fast return of the extremity motor function and sensation feeling to normal functioning at the end of the surgery. Such quick recovery enables patients to be discharged earlier [1,2]. However, this method has also disadvantages such as tourniquet pain, insufficient muscle relaxation, insufficient postoperative analgesia and local anesthetic toxicity [3].

In order to prevent disadvantages with IVRA, many adjuvant drugs have been added to local anesthetics to obtain better intraoperative anesthesia, to prevent tourniquet pain and to prolong postoperative analgesia [4-8]. In many studies in the literature, IVRA has been combined with adjunctive drugs such as ketorolac [4], NSAIDs [5,7], paracetamol [6], ketamine [8], opioids [9] and α-2 adrenergic receptor agonists [10]. Various NSAID studies have demonstrated successful improvement in analgesia when added to lidocaine in IVRA. Opioid studies (on morphine and tramadol) have shown that the addition of opioids to IVRA improves postoperative analgesia compared with placebo adjuvant. On the other hand, the combination of lidocaine IVRA with morphine or tramadol has been reported to improve postoperative analgesia and sensory block, albeit not providing any advantages on tourniquet pain, motor block quality, analgesia duration or analgesic consumption [9].

There are no clinical studies in the literature to the best of our knowledge comparing the efficacy of lornoxicam and fentanyl when added to lidocaine IVRA, or efficacy of opioid drug fentanyl as an adjuvant added to lidocaine IVRA.

In our current study, we hypothesized that fentanyl should have a more favorable effect in minimizing intraoperative tourniquet pain than lornoxicam. However, due to long half-life lornoxicam could have a longer analgesic effect at the postoperative period when compared to fentanyl. Our primary outcome was first analgesic requirement time. Our secondary outcomes were tourniquet pain and sensory block recovery time at postoperative period.

Method

The local ethics committee of Ege University Hospital approved this double blind randomized study. We informed all patients about the study protocol and obtained written informed consent.

Patients who were between the ages of 18 and 60, whose ASA physical states were I-II, who were scheduled to undergo outpatient hand surgery due to carpal tunnel syndrome, Dupuytren's contracture, trigger finger and ganglion cyst were recruited for the current study. We excluded from the study the patients who had uncontrolled hypertension, epilepsy, diabetic neuropathy, Reynaud's disease, drug and local analgesic allergies or opioid addiction. The study began January 2010 and ended May 2010 and, in this time frame, a total of 45 patients were included.

We monitored heart rate (HR), mean arterial pressure (MAP) and peripheral oxygen saturation (SpO_2) of patients in the operating room (Hewlett Packard -Viridia 24C France). We attached a double-cuff tourniquet to the arm to be operated. In order to inject local anesthetic on the arms that would be operated, a 24G cannula was inserted in a vein on the dorsal hand. Another IV, 20G cannula was prepared for fluid infusion on the other hand.

In the operative upper extremity, we drained the veins by lifting them up for 3 minutes and tightly wrapping the arm with Esmarch bandage until the distal cuff of the tourniquet. Afterwards, we inflated a double-cuff pneumatic tourniquet (VBM Medizintechnik GmbH Germany) until the proximal cuff pressure was at least 100 mmHg more than the systolic arterial pressure (minimum 250 mm Hg). Then the Esmarch bandage was removed. As a result we observed loss of radial pulse, trace loss in the pulse oximetry and absence of circulation in the arm. Then, we injected a local anesthetic and adjuvant mixture through the vascular access at the operative extremity. A physician who was blinded to the randomization scheme provided intraoperative and postoperative evaluations.

Patients were randomized into three groups based on a computer generated, random number sequence and sealed envelopes. Patients in Group I (L) received 3 mg.kg^{-1} lidocaine 40 mL (2% Lidocaine, Aritmal, Biosel, Turkey); patients in Group II (LL) received 3 mg.kg^{-1} lidocaine 38 mL + 2 mL lornoxicam (4 mg.mL^{-1} Lornoxicam, Xefo, Abdi Ibrahim, Turkey); patients in Group III (LF) received 3 mg.kg^{-1} lidocaine 38 mL + 2 mL fentanyl (0.05 mg.mL^{-1} Fentanyl citrate, Hospira, USA). The local anesthetic with adjuvant drug mixture was administered via slow IV infusion over 2 minutes to the extremity with no circulation. The distal cuff on the upper arm was inflated 10 minutes after the administration of the drug, then, the proximal cuff was deflated.

We evaluated patients' motor and sensory block as follows: motor block in finger and wrist movements as: 0 = no motor impairment, 1 = partial power loss, 2 = complete power loss ; sensory block was evaluated with the pinprick test performed every minute using a 22G needle on the radial, median, ulnar, lateral and medial antebrachial cutaneous nerves.

We recorded times as follows [11]:

Motor block onset time:	Time elapsed from the injection of the drug until complete power loss in hand and wrist was established
Sensory block onset time:	Time elapsed from the injection of the drug until complete sensory block was established in all dermatomes
Motor block recovery time:	Time elapsed from the removal of the tourniquet to the initiation of motor movement in hand and wrist
Sensory block recovery time:	Time elapsed from the removal of the distal tourniquet until the disappearance of complete sensory block in all dermatomes

Analgesia duration:	Time elapsed from the opening of the tourniquet until the start of the initial pain

VAS scores at 5, 10, 15, 20, 25, and 30 minutes were evaluated and recorded after the proximal tourniquet on the upper arm was deflated and distal tourniquet was inflated. For those who had VAS above 4, a total of 1 $\mu g.kg^{-1}$ IV fentanyl was administered. In patients who continued to have pain despite this, general anesthesia with a laryngeal mask was used and recorded. Intraoperative hypotension (25% lower than basal) was treated with 5 mg IV ephedrine, bradycardia (25% of basal) was treated with 0.5 mg IV atropine. The patients who had nausea and vomiting were treated with 4 mg IV ondansetron. Those with 95% oxygen saturation were given 5 $L.min^{-1}$ oxygen supports via mask and recorded. Patient satisfaction was evaluated at the end of the operation as follows [11]:

4- Excellent: No complaint from the patient

3- Good: Minor complaint with no need for supplemental analgesics

2- Moderate: Complaint, which required supplemental analgesic (fentanyl IV 1 $\mu g.kg^{-1}$).

1- Unsuccessful: Patient transitioned to general anesthesia.

Tourniquet pressure was released with several minute intervals and at least 30 minutes after the drug injection.

We recorded postoperative pain scores (VAS) at 30 minutes, and 1, 2, 4, 6, and 24 hours. MAP, HR and sedation scores were also recorded at same time points. Those with VAS > 4 were given IV paracetamol. Patient who continued to have pain after paracetamol, were given 50 mg IV meperidine. In addition, we observed local anesthetic toxicity and postoperative opioid drug side effects such as nausea, vomiting, skin rash, tinnitus, convulsion in patients. Then, we conducted a 24^{th} hour postoperative check up by calling the patients at home and recording results.

In the current study, our primary outcome was first analgesic requirement time. Sample size calculation was based on first analgesic requirement time. Therefore, to reach statistically significant difference between three groups a sample size was calculated by accepting an alpha risk of 5% and a power (1-β) of 99%. From this calculation, 15 subjects in each group would be necessary for a significant difference ($p < 0.05$). Statistical analysis was conducted using computer software package SPSS 16.0 (SPSS Inc., Chicago, Illinois). We summarized data as mean ± standard deviation. In order to analyze differences between groups based on numeric variables that show normal distribution, we used the ANOVA test and then Bonferroni's correction. For repeated measurements, we used a variance analysis. In comparison of categorical data groups, cross tables were formed and Chi-Square test was used. In the analysis of variables not showing normal distribution we used the Kruskal Wallis and the Mann-Whitney U tests. In all tests, p value < 0.05 was considered statistically significant.

Results

Table 1 shows patients' demographic and perioperative data, onset and recovery times of sensory and motor blocks. Demographical characteristics of the patients in three groups did not show statistically significant difference. In addition, three groups did not show any significant difference in terms of operation and tourniquet times ($p > 0.05$, Table 1).

Motor and sensory block onset times, motor block recovery time and degree of motor block were similar between three groups, but the difference in terms of sensory block recovery time and first analgesic requirement time were statistically significant between three groups (Table 1). The difference was due to the comparison of Group I and Group II (for sensory block recovery time $p < 0.001$; for first analgesic requiring time $p < 0.001$) and Group II and Group III (for sensory block recovery time $p < 0.001$; for first analgesic requiring time $p < 0.001$). Group II had both longer sensory block recovery time and first analgesic requirement time than the other two groups. No significant difference was

Table 1 - Demographic and Perioperative Data and Onset and Recovery Times of Sensory and Motor Blocks.

	GROUP I	GROUP II	GROUP III	p
Age (year)	50 ± 12	50 ± 10	48 ± 16	0.846
Height (cm)	166 ± 6	165 ± 8	164 ± 9	0.765
Weight (kg)	78 ± 14	75 ± 11	74 ± 18	0.761
ASA(I/II)	7/8	7/8	6/9	0.914*
Operation Time (min)	23 ± 3	22 ± 2	22 ± 2	0.765
Turniquet Time (min)	30 ± 3	29 ± 3	29 ± 3	0.859
Motor block onset time (min)	9.0 ± 1.81	8.93 ± 1.62	8.73 ± 1.58	0.902
Sensory block onset time (min)	6.53 ± 1.68	6.73 ± 1.58	6.73 ± 1.49	0.924
Sensory block recovery time (min)	21.0 ± 5.41	30.7 ± 3.37	23.67 ± 4.22	p < 0.001
Motor block recovery time (min)	6.0 ± 1.13	5.73 ± 1.16	6.13 ± 1.36	0.66
First analgesia requiring time (min)	26.3 ± 7.7	41 ± 6.04	27.7 ± 5.6	p < 0.001
Intraoperative analgesia need (# patients)	3	2	0	0.34*

Three groups compared with ANOVA; *Chi square and Fisher's Exact tests results.

Table 2 - Pairwise Comparisons of Intraoperative and Postoperative VAS Scores.

Time intervals	Group I vs Group II	Group I vs Group III	Group II vs Group III
TPVAS 5 (min)	p = 0.2	p = 0.002*	p = 0.07
TPVAS 10 (min)	p = 0.19	p = 0.002*	p = 0.069
TPVAS 15 (min)	p = 0.06	p = 0.001*	p = 0.12
TPVAS 20 (min)	p = 0.09	p = 0.005*	p = 0.18
TPVAS 25 (min)	p = 0.05	p = 0.003*	p = 0.28
TPVAS 30 (min)	p = 0.09	p = 0.003*	p = 0.19
TRVAS 30 (min)*	p = 0.002	p = 0.008	p = 0.61
TRVAS 1 (hour)	p = 0.23	p = 0.44	p = 0.73
TRVAS 2 (hour)	p = 0.18	p = 0.13	p = 0.93
TRVAS 3 (hour)	p = 0.53	p = 0.27	p = 0.83
TRVAS 4 (hour)*	p = 0.005	p = 0.01	p = 0.78
TRVAS 6 (hour)	p = 1.0	p = 1.0	p = 1.0
TRVAS 24 (hour)	p = 1.0	p = 1.0	p = 1.0

Mann-Whitney U test result, *p < 0.05. TPVAS: tourniquet pain VAS (intraoperative), TRVAS: tourniquet release VAS (postoperative).

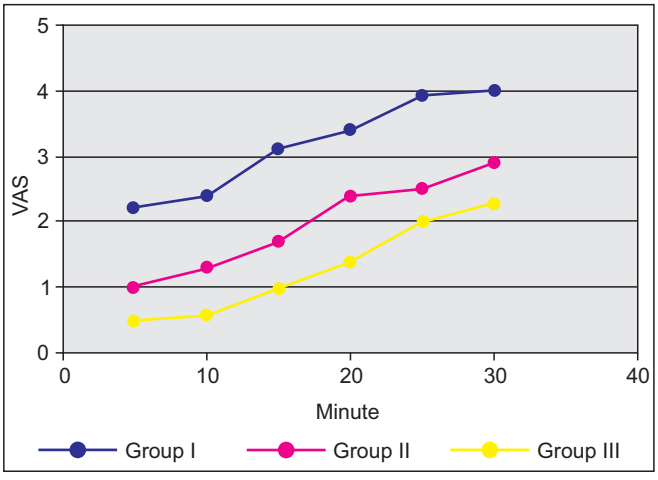

Figure 1 Intraoperative (tourniquet pain) VAS.

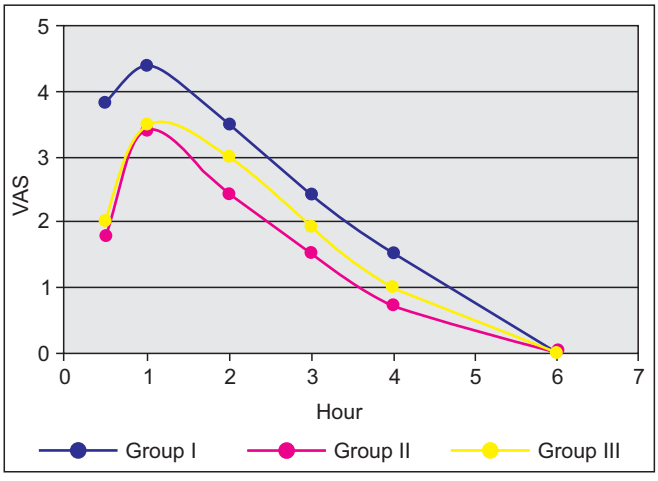

Figure 2 Postoperative VAS.

obtained in terms of sensory block recovery time and first analgesic requirement time from the comparison of Group I and Group III (Table 1).

Comparison of intraoperative tourniquet VAS scores revealed significant differences between three groups (Figure 1). Pairwise comparisons revealed that the difference was due to comparison of Group I and Group III. No significant differences were observed in terms of VAS scores at each time interval from the comparisons of Group I and Group II and Group II and Group III (Table 2).

Regarding postoperative VAS scores, the scores at 30 minutes and 4 hours after operation were significantly different between three groups (p = 0.004 and p = 0.01 respectively, Figure 2). For both time intervals, the difference was due to the comparison of Group I versus Group II and Group I versus Group III (Table 2). No statistically significant difference was found between group II and Group III in terms of VAS scores at 30 minutes and at 4 hours postoperatively.

Table 3 - Complications and Patients' Satisfaction from the Procedure.

	Group I	Group II	Group III	P
Nausea	0	0	2	0.12
Vomiting	0	0	1	0.36
Tinnitus	1	1	1	-
Itching	0	0	3	0.04*
Convulsion	0	0	0	-
Rescue analgesia	3	2	0	0.21
Patient satisfaction (1/2/3/4)	2/2/5/6	0/1/4/10	0/2/5/8	0.47

Chi square and Fisher's Exact tests results. *p < 0.05.

There was no statistically significant difference in the MAP, HR values between the three groups at any time during the study (p > 0.05).

When the groups were analyzed based on intraoperative and postoperative side effects, there was one case of local anesthetic systemic toxic reaction with tinnitus and nearly fainting as symptoms in each group. In Group III, we observed opioid side effects such as nausea, vomiting and itching (Table 3). Hemodynamic instability was not observed in any of the patients. In regards to the need for postoperative additional analgesia (rescue analgesia), no significant difference was observed between groups (p = 0.2, Table 3).

Discussion

The main findings of our study were: addition of NSAID lornoxicam to lidocaine IVRA increased the sensory block recovery time without increasing side effects and increased first analgesic requirement time compared to lidocaine IVRA as well as fentanyl added to lidocaine IVRA. In addition, we found that fentanyl added to lidocaine IVRA showed better intra-operative analgesic effect (decreased tourniquet pain) than lidocaine IVRA but showed similar analgesic effect when compared to lornoxicam added to lidocaine IVRA. However, lornoxicam added to lidocaine IVRA was not superior to lidocaine IVRA in decreasing tourniquet pain.

Intravenous lidocaine interacts with peripheral and central voltage-gated Na^+ channels, in the intracellular side of the cell membrane. Intravenous lidocaine affects peripheral and central nerve endings. Data in the literature indicate that central sensitization resulting from tissue damage would be minimized by lidocaine in different levels of the nervous system depending on the damage. Intravenous lidocaine administration increases the acetylcholine (Ach) concentration in the cerebrospinal fluid and analgesic effect of lidocaine is thought to be the result of binding Ach to muscarinic M3 receptors, by inhibition of glycine receptors and by releasing endogenous opioids, which would exacerbate the inhibitory descending pain pathways resulting in analgesia. Intravenous lidocaine reduces the inflammatory response to tissue ischemia and attenuates the tissue damage induced by endothelial and vascular cytokines through a mechanism involving the release of adenosine triphosphate and K^+ channels [12].

In the current study we found that lornoxicam added to lidocaine IVRA improved sensory block and postoperative analgesia compared to lidocaine IVRA and fentanyl added to lidocaine IVRA. This finding was in line with the prior lornoxicam study findings and the NSAID study findings [5,7].

Lornoxicam is a NSAID from the oxicam category that has analgesic and anti-inflammatory effects. Lornoxicam blocks cyclooxygenase-2 enzyme (COX-2) which inhibits prostaglandins that are responsible for recognition and transduction of pain stimulation. The inhibition of prostaglandin synthesis by NSAIDs has been demonstrated to effectively reduce inflammatory symptoms such as edema and pain. COX-2 is an inducible molecule that takes several hours to induce inflammatory pain. Therefore only COX-2 inhibition properties of lornoxicam do not explain its analgesic effects. Other mediators of inflammation such as reactive oxygen products and cytokines have also been shown to contribute to inflammation and inflammatory pain. By induction of COX-2 gene nitric oxide synthase is induced and it leads to increased levels of nitric oxide in inflamed tissues. Nitric oxide has been shown to contribute to edema formation, hyperalgesia and pain. Another important element of the pro-inflammatory process is the presence of cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and IL-8. Berg et al. investigated the effect of lornoxicam on human COX-1 and human COX-2, on nitric oxide synthase and on the formation of TNF-α, IL-1β, IL-6, and IL-8 and they found that lornoxicam inhibited COX-isoenzymes equipotently and inhibited IL-6 and nitric oxide production, thus all these effects of lornoxicam are the result of its anti-inflammatory

and analgesic effect [13]. In the current study, we did not observe short-term analgesic effects of lornoxicam. Thus lornoxicam did not provide good quality of analgesia in terms of tourniquet pain. Therefore, this finding was not comparable with the findings emphasizing the advantages of lornoxicam on tourniquet pain [14]. Lornoxicam is rapidly eliminated, having a plasma elimination half-life of 3-5 hours [13]. In our study, favorable analgesic effect of lornoxicam was limited to four hours as shown by postoperative VAS scores, which were congruent with lornoxicam's elimination half-life.

Our study also evaluated the intraoperative and postoperative analgesic effects of fentanyl when added to lidocaine IVRA. Opioids have central effects and are synthesized especially after tissue damage as a result of activated opioid receptors. Due to these peripheral effects, using opioids combined with local anesthetics have increased in regional anesthesia applications [15]. The results of the studies concerning the analgesic effects of opioids (morphine and tramadol) are scarce and, based on the studies regarding the addition of morphine to the local anesthetic in IVRA, we did not find that increasing the dose of morphine increased intraoperative and postoperative analgesic effect [9,15,16].

Our study is the first that observed analgesic effects of fentanyl in IVRA. Although fentanyl is a more potent analgesic than lornoxicam, we could not show advantages of fentanyl on tourniquet pain as compared to lornoxicam in current study. This could be due to the small sample size. In addition, we did not show superiority of fentanyl in terms of postoperative analgesic need when compared to lornoxicam added to lidocaine IVRA and to lidocaine IVRA. This may be due to fentanyl's short half-life.

After the tourniquet deflation, local anesthetic toxicity risk increases due to the rapid diffusion of large amounts of the local anesthetic into the circulation. For this reason, the local anesthetic amounts used should be limited to minimal effective dose to provide surgical anesthesia. This, in turn, increases the need for additional analgesics. We have achieved adequate anesthesia and analgesia by adding lornoxicam and fentanyl. However, further studies are needed if lower dose of local anesthetic combinations may also provide similar anesthesia quality.

There are some limitations to our current study. The drug doses selected were chosen from the literature. Lornoxicam and fentanyl doses were chosen from previous studies. Although a higher dose of fentanyl and lornoxicam might provide better intraoperative and postoperative analgesia, more side effects could be observed. Another limitation is small sample size, which may decrease the generality of our results.

In conclusion, when fentanyl is added to lidocaine, intraoperative tourniquet pain is decreased in expense of opioid-related side effects. However, lornoxicam does not increase side effects while providing additional intraoperative and postoperative analgesia. Therefore, lornoxicam can be accepted as a better adjunctive drug than fentanyl in IVRA.

Acknowledgment

We thank Alparslan Turan, MD (University of Louisville), for his invaluable help in the preparation of the final manuscript and Mehmet Orman, MD (Ege University School of Medicine, Department of Biostatistics) for monitoring the data and performing the statistical analysis.

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