The analgesic effect of lornoxicam when added to lidocaine for intravenous regional anaesthesia

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Background. The aim of the study was to evaluate the effect of lornoxicam (L) on sensory and motor block onset time, tourniquet pain, and postoperative analgesia, when added to lidocaine in intravenous regional anaesthesia (IVRA).

Methods. Forty-five patients undergoing hand surgery were randomly and blindly divided into three groups as to receive either i.v. saline and IVRA with lidocaine 0.5% (Control group, n=15), i.v. saline and IVRA lidocaine 0.5% with lornoxicam (L-IVRA group, n=15), or intravenous lornoxicam and IVRA lidocaine 0.5% (L-IV group, n=15). Sensory and motor blocks onset time, and tourniquet pain was measured after tourniquet application at 5, 10, 20, and 30 min, and analgesic use were recorded during operation. After the tourniquet deflation, at 1, 30 min, and 2, 4 h, visual analogue scales score, the time to first analgesic requirement, total analgesic consumption in first 24 h, and side effects were noted.

Results. Sensory and motor block onset times were shorter and the recovery time prolonged in the Group L-IVRA compared with the other group (P=0.001). A decreased tourniquet pain, a prolonged time first analgesic requirement [229 (85) min vs 28 (20) and 95 (24) min, P=0.0038] and less postoperative analgesic requirements during 24 h were found in Group L-IVRA compared with the other groups (P<0.05).

Conclusions. The addition of lornoxicam to lidocaine for intravenous regional anaesthesia shortens the onset of sensory and motor block, decreases tourniquet pain and improves postoperative analgesia without causing any side effect.

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Intravenous regional anaesthesia (IVRA) was first described in 1908 for anaesthesia of the hand and forearm by August Karl Gustav Bier.1 It is easy to administer, reliable and cost-effective for short operative procedures of extremities performed on an ambulatory basis.1,2 Different additives have been combined with local anaesthetics (LAs) to improve block quality, prolong post-deflation analgesia, and decrease tourniquet pain.1–4 Although various NSAIDs have been demonstrated to improve analgesia such as ketorolac,5–7 tenoxicam8 and aspirin9 in IVRA, there is no clinical study evaluating lornoxicam when added to lidocaine for IVRA to the best of our knowledge.

Lornoxicam is a new NSAID of the oxicam class with analgesic, anti-inflammatory and antipyretic properties which is available in oral and parenteral form.10 It is rapidly eliminated, having a short plasma elimination half-life of 3–5 h,10,11 which suggests its suitability for acute use in the postoperative period.11,12 Lornoxicam is also as effective as morphine but better tolerated when administered intravenously by patient-controlled analgesia in the treatment of moderate postoperative pain after laminectomy or discectomy.13 Furthermore, wound infiltration with a combination of LA plus lornoxicam improved postoperative pain control and patient comfort, and decreased the need for opioid as compared with the use of either drug alone suggesting a local effect.14

We planned this study to evaluate the effect of lornoxicam on intra- and postoperative analgesia; sensory and motor block onset times when added to lidocaine for IVRA. Our primary endpoint was the intraoperative pain
control, i.e. the time until tourniquet pain required the use of supplemental fentanyl.

Methods
This prospective, randomized and double-blinded study was performed in 45 ASA I–II patients scheduled for hand or forearm surgery (i.e. carpal tunnel, trigger finger, and tendon release). Informed consent and ethical committee approval was obtained. Patients with sickle cell anaemia, or history of drug allergy, and Raynaud disease were excluded from the study. Patients were premedicated with i.m. midazolam 0.15 mg kg\(^{-1}\) and atropine 0.01 mg kg\(^{-1}\) administered before the surgical procedure. After the patients had been taken to the operating room, mean arterial blood pressure (MAP), peripheral oxygen saturation (Sp\(_{O2}\)), and heart rate (HR) were monitored (Datex-Ohmeda AS-3, Finland). Two cannula were placed; one in a dorsal vein of the operative hand and the other in the opposite hand for crystalloid infusion. The operative arm was elevated for 2 min then exsanguinated with an Esmarch bandage; a pneumatic tourniquet was then placed around upper arm, and proximal cuff was inflated to 250 mm Hg. Circulatory isolation of the arm was verified by inspection, absence of radial pulse, and loss of pulse oximetry tracing in the ipsilateral index finger. Identical syringes containing each drug were prepared according to the study design and randomization of patients according to a computer generated list; drugs were prepared and concealed by a resident not involved in any other part of the study. An anaesthesiology resident blinded to the group and drug allocation applied the concealed syringes and recorded all data. The syringes contained 3 mg kg\(^{-1}\) lidocaine 2% (Arimtal; TEMS, Turkey) diluted with saline to a total volume of 40 ml in all groups for IVRA. Patients were assigned at random to one of three groups: (i) Control group received saline 0.9% 2 ml (NS) i.v. and NS was added to the IVRA solution; (ii) Group L-IVRA received NS i.v. and lornoxicam (Xefo, Abdi Ibrahim Ilac San., Turkey) 8 mg was added to the IVRA solution; and (iii) Group L-IV received lornoxicam 8 mg i.v. and NS again was added to the IVRA solution. All solutions administered i.v. were given 8 (range 5–10) min before inflation of the operative tourniquet, into an i.v. line established in the non-operative arm.

The sensory block was assessed by a pinprick performed with a 22-gauge short-bevelled needle every 30 s. Patient response was evaluated in the dermatomal sensory distribution of the medial and lateral antebraclial cutaneous, ulnar, mean, and radial nerves. Motor function was assessed by asking the subject to flex and extend his/her wrist and fingers, and complete motor block was noted when no voluntary movement was possible.

Sensory block onset time was noted as the time elapsed from injection of drug to sensory block achieved in all dermatomes. Motor block onset time was the time elapsed from injection of drug to complete motor block.

The IVRA drugs were given after the proximal cuff was inflated to 250 mm Hg. The surgery was started 10 min after the distal tourniquet inflation in all patients. MAP, HR, Sp\(_{O2}\), and visual analogue scale (VAS) scores (0=no pain and 10=worst pain imaginable) were monitored before and after tourniquet application, at 5, 10, 20 and 30 min after injection of the anaesthetics. Data were measured after release of the tourniquet; and postoperative 30 min and 2, 4, 6 and 24 h by an anaesthesiology resident who was blinded to study. When pain due to tourniquet was >3 on the VAS, patients were given fentanyl 1 \(\mu\)g kg\(^{-1}\) (Fentanyl Citrate; Abbott), and the total administered dose and requirement time were noted. At the end of the operation, patients were asked to qualify the operative conditions such as tourniquet pain or incisional pain according to the following numeric scale: excellent (4)=no complaint from pain; good (3)=minor complaint with no need for supplemental analgesics; moderate (2)=complaint which required supplemental analgesic; and unsuccessful (1)=patient given general anaesthesia.

At the end of the operation, the surgeon, who was blind to patient group, was asked to score operative conditions such as disturbing movement of the arm and excessive bleeding according to the following numeric scale: 0=unsuccessful; 1=poor; 2=acceptable; 3=good; and 4=excellent (4).

The tourniquet was not deflated before 30 min and was not inflated for more than 1 h. At the end of surgery, the tourniquet deflation was performed by the cyclic deflation technique. Sensory recovery time was noted (time elapsed after tourniquet deflation up to recovery of pain in all dermatomes determined by pinprick test). Motor block recovery time was noted (the time elapsed after tourniquet deflation up to movement of fingers).

Postoperatively patients were instructed to receive 75 mg diclofenac i.m. (Voltaren; Ciba-Geigy, Istanbul, Turkey) when VAS was >3, and the total diclofenac consumption was recorded in the first 8 h postoperatively. Patients were given paracetamol (Parol tablet 500 mg; Abtabay, Istanbul, Turkey) by oral route, in postoperative 8–24 h, when VAS was >3, and the total administered paracetamol dose was noted. All evaluations were performed by an anaesthesia resident blinded to the study. The time to first analgesic requirement (the time elapsed after tourniquet release to first patient request of analgesic) was also noted. Patients were questioned about side effects during the first 2 h in the postanaesthesia care unit and later in the ward every 2 h by an anaesthesia resident who was blinded to the study. Skin rash, gastric discomfort, tinnitus, nausea and other side effects were noted if encountered during the first 24 postoperative hours in the ward.

Statistical analyses
The sample size estimation was based on a pilot study with 10 cases per group. These data are not included in this analysis. Two sample size estimations were performed.
Results

Demographic data of the groups were similar for mean age, weight, and sex ratio (Table 1). There was no exclusion from the study because of technical failure. There was no significant difference in types of surgical procedure, and duration of surgery and tourniquet time (Table 1).

There was also no statistical difference between groups when compared for mean arterial pressure, heart rate and saturation at any intraoperative and postoperative period ($P>0.05$).

Sensory and motor block onset times were shorter while recovery times were prolonged in L-IVRA group compared with the other groups (Table 2). No patient suffered from incisional pain during intraoperative period in all groups. Supplemental fentanyl was required for tourniquet pain in 7 patients in Group Control and 6 patients in Group L-IV, but only in one patient in Group L-IVRA ($P=0.012$). The first fentanyl requirement time for tourniquet pain was also prolonged in Group L-IVRA when compared with the other groups ($P=0.042$) (Table 3). The amount of intraoperative fentanyl requirements for tourniquet pain were also lower in Group L-IVRA than the other groups ($P=0.014$) (Table 3). VAS scores of tourniquet pain were higher at 10, 20, 30 min in Control and L-IV groups when compared with Group L-IVRA (Table 4). Postoperative VAS scores were higher for the first 2 h in Control and Group L-IV than Group L-IVRA (Table 4). VAS scores are presented in Figure 1 (no statistically significant differences were observed).

Anaesthesia quality, determined by the patient and the surgeon, was better in Group L-IVRA (Table 5). The time to first postoperative analgesic request in Group L-IVRA was longer than the Control and L-IV groups [in Group L-IVRA, 229 (85) min vs 28 (20) and 95 (24) min respectively in the other groups, $P=0.0038$]. Diclofenac consumption was lower in the Group L-IVRA [15 (31) mg] compared with Group Control [85 (26) mg] and

| Table 2 Onset and recovery times of sensory and motor block. *$P<0.001$, **$P=0.001$ for Group L-IVRA vs other groups. Values are shown as mean (SD). The groups are presented as to receive either i.v. saline and IVRA with lidocaine 0.5% (Control group, n=15), i.v. saline and IVRA lidocaine 0.5% with lornoxicam (L-IVRA group, n=15), or i.v. lornoxicam and IVRA lidocaine 0.5% (L-IV group, n=15). |
|-----------------|-----------------|------------------|
| Variable        | Group Control   | Group L-IVRA     | Group L-IV       |
|                 | (n=15)          | (n=15)           | (n=15)           |
| Sensory block onset time (min) | 4.2 (1.1) | 2.1 (0.8)* | 4.0 (1.2) |
| Sensory block recovery time (min) | 3.3 (1.5) | 7.5 (1.3)* | 3.6 (1.8) |
| Motor block onset time (min) | 4.9 (1.2) | 2.2 (0.8)* | 4.3 (1.5) |
| Motor block recovery time (min) | 3.5 (0.7) | 6.6 (1.4)* | 3.7 (0.9) |

| Table 3 Intraoperative fentanyl requirement for tourniquet pain. The groups are presented as to receive either i.v. saline and IVRA with lidocaine 0.5% (Control group, n=15), i.v. saline and IVRA lidocaine 0.5% with lornoxicam (L-IVRA group, n=15), or i.v. lornoxicam and IVRA lidocaine 0.5% (L-IV group, n=15). Values are shown as mean (SD). |
|-----------------|-----------------|------------------|
| Variable        | Group Control   | Group L-IVRA     | Group L-IV       |
|                 | (n=15)          | (n=15)           | (n=15)           |
| Intraoperative fentanyl amount (µg) | 23.3 (25.8) | 3.3 (12.9)* | 19.4 (18.6) |
| Intraoperative fentanyl requirement time (min) | 15.8 (6) | 28 (9)* | 13.6 (8) |
Group L-IV [67 (36) mg] (P<0.0001). Paracetamol consumption was also lower in Group L-IVRA [200 (253) mg] than the Control [1400 (207) mg] and L-IV groups [1100 (320) mg] (P<0.0001).

No patient developed intraoperative excessive bleeding or postoperative gastric discomfort or nausea as side effects (P>0.05).

**Discussion**

The main result of our study was that addition of lornoxicam to lidocaine for IVRA decreased tourniquet pain, improved the speed of onset and the quality of anaesthesia, decreased intraoperative and postoperative analgesic consumption, without causing any side effect.

Alkalization with bicarbonate has been investigated as an adjunct for IVRA. LA exists in two forms: the non-ionized, lipid-soluble free base and the water-soluble ionized form. The relative proportions of each depend upon the pKₐ of the drug and the pH of the environment (nearby tissue). The pKₐ of a LA (for lidocaine as 7.8) is fixed but, by increasing the pH of a solution, it is possible to increase the percentage of free base and thus improve the nerve penetration and the rate of onset of blockade. The pH value of lornoxicam intravenous form is approximately 8.7. In our study, the pH of lornoxicam–lidocaine mixture was measured as 7.6 and the pH of the lidocaine solution alone was 6.7. It is thus possible that alkalization of LA

**Table 4** Intraoperative (tourniquet pain) and postoperative visual analogue scale (VAS) scores. Values are shown as means (range). *P=0.006, **P=0.030, ***P=0.002, †P=0.003, ‡P=0.014, and §P=0.031 among the groups. Data are mean (range).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group Control (n=15)</th>
<th>Group L-IVRA (n=15)</th>
<th>Group L-IV (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min after tourniquet inflation</td>
<td>1.13 (0–3)</td>
<td>0.53 (0–2)</td>
<td>1.06 (0–3)</td>
</tr>
<tr>
<td>10 min after tourniquet inflation</td>
<td>1.46 (0–4)</td>
<td>0.60 (0–2)*</td>
<td>2.06 (0–4)</td>
</tr>
<tr>
<td>20 min after tourniquet inflation</td>
<td>2.46 (1–5)</td>
<td>1.33 (0–3)**</td>
<td>2.42 (0–5)</td>
</tr>
<tr>
<td>30 min after tourniquet inflation</td>
<td>2.73 (1–5)</td>
<td>1.60 (0–3)**†</td>
<td>2.80 (2–5)</td>
</tr>
<tr>
<td>Tourniquet release (after 30 min)</td>
<td>3.33 (1–5)</td>
<td>1.73 (1–4)**</td>
<td>3.13 (2–5)</td>
</tr>
<tr>
<td>Tourniquet release (after 2 h)</td>
<td>3.13 (2–5)</td>
<td>2.06 (1–4)**</td>
<td>2.8 (2–5)</td>
</tr>
<tr>
<td>Tourniquet release (after 4 h)</td>
<td>2.6 (1–5)</td>
<td>2.0 (1–3)**</td>
<td>2.93 (1–5)</td>
</tr>
<tr>
<td>Tourniquet release (after 4 h)</td>
<td>3.2 (2–4)</td>
<td>2.9 (1–4)</td>
<td>3.06 (2–4)</td>
</tr>
</tbody>
</table>
Table 5 Quality of anaesthesia assessed by patients, and surgeon. Values are shown as means (range). $^*P<0.022$, $^9P=0.008$ among the groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group Control (n=15)</th>
<th>Group L-I (n=15)</th>
<th>Group L-IV (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of anaesthesia (patient)</td>
<td>3.4 (3–4)</td>
<td>3.8 (3-4)$^*$</td>
<td>3.4 (3–4)</td>
</tr>
<tr>
<td>Quality of anaesthesia (surgeon)</td>
<td>3.4 (3–4)</td>
<td>3.9 (3–4)$^9$</td>
<td>3.5 (3–4)</td>
</tr>
</tbody>
</table>

with lornoxicam might contribute to faster sensory and motor block onset times by increasing the proportion of free base. This mechanism might also explain why the onset time of sensory and motor blocks were shorter in Group L-I compared with Group L-IV. Prolonged motor blockage may provide a safe clinical condition following tourniquet release by preventing a large amount of local anesthetic entering the systemic circulation with arm movement.

Reuben and colleagues$^6$ have demonstrated the potential intraoperative benefit of NSAIDs added to LA. They compared with tourniquet pain scores and found significantly fewer patients had a pain score of $>3/10$ during the first 30 min when ketorolac 60 mg was added in IVRA. In another study, Reuben and Duprat$^8$ also explained that NSAIDs decrease the synthesis of inflammatory mediators and afferent nociceptive signals arising from the site of surgery. The major analgesic effect of NSAID is assumed to be due to COX-2 inhibition. COX-2 is an inducible molecule which takes several hours to induce inflammatory pain,$^{16}$ which is in contrast to clinical observations like our results where adding lornoxicam to IVRA has apparently such an immediate onset of action. Therefore, it must be assumed that another mechanism is involved. For example, the role of A-delta fibres and unmyelinated C-fibres may be considered to be involved in tourniquet pain because of the circumferential compression of peripheral nerves enhanced by ischemia.$^3$ Although C fibres are more resistant to LA than A-delta fibres,$^{17}$ NSAIDs may prevent conduction of C fibres.$^{18}$ Also, opening of the $K^+$ channels located in the primary afferent nerve endings produces antinociception and represents an important step in the peripheral antinociceptive effect of several NSAIDs.$^{18}$ Activation of the NO–cyclic GMP pathway could also induce antinociception through the opening of $K^+$ channels.$^{18,19}$ Lornoxicam might produce a peripheral analgesic effect via NO–c GMP pathway and the opening of $K^+$ channels. Buritova and Besson also suggested that lornoxicam shows antinociceptive effect in predominantly peripheral site.$^{20}$ These mechanisms may explain why the analgesic effect of lornoxicam in IVRA was better than the systemic administration for tourniquet pain.

It was also suggested that tourniquet pain may arise from ischaemia and oxidative stress.$^{21}$ Codere and colleagues$^{22}$ suggested that antioxidant therapy such as $N$-acetyl-l-cysteine may reduce experimental ischaemic pain due to oxidative damage. Antioxidants for pain treatment may also decrease the dose of analgesics and prevent the negative impact of reactive oxygen species on nociception.$^{23}$ Lornoxicam shows antioxidative effects in rats,$^{24}$ thus it is also possible that local administration of lornoxicam might attenuate tourniquet pain by antioxidative mechanism.

Clinical studies have demonstrated an enhanced analgesic effect from NSAIDs when concentrated at a peripheral site compared with the systemic administration of the same drug.$^7$ Reuben and Duprat$^8$ reported that patients had less pain during the first postoperative hour, required no supplemental analgesia in the post anaesthesia care unit and consumed fewer analgesics during the first postoperative day when ketorolac was added to standard LA in their study. They also suggested that this derived from residual ketorolac in the operative arm, and some redistribution of ketorolac to the systemic circulation would be expected to occur after tourniquet deflation, possibly producing some late analgesia.$^7$ It might be related to our findings as prolonged postoperative analgesia and less analgesic requirement.

In conclusion, addition of lornoxicam to lidocaine in IVRA shortens sensory and motor block onset times, prolongs sensory and motor block recovery times, and improves tourniquet pain while it prolongs first analgesic requirement time, and decreases total amount of analgesic. The underlying mechanisms are yet to be elucidated with more experimental studies.

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