Regional Anesthesia for Postoperative Pain Control

Guest Editors: Ahmet Eroglu, Engin Erturk, Alparslan Apan, and Ozgun Cuvas Apan
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Contents

Regional Anesthesia for Postoperative Pain Control, Ahmet Eroglu, Engin Erturk, Alparslan Apan, Urs Eichenberger, and Ozgun Cuvas Apan
Volume 2014, Article ID 309606, 2 pages

Does the Addition of Tramadol and Ketamine to Ropivacaine Prolong the Axillary Brachial Plexus Block?, Ahmet Can Senol, Ozlem Uknife, and Alper Timurkaynak
Volume 2014, Article ID 686287, 5 pages

Volume 2014, Article ID 631756, 7 pages

Efficacy of Continuous Epidural Analgesia versus Total Intravenous Analgesia on Postoperative Pain Control in Endovascular Abdominal Aortic Aneurysm Repair: A Retrospective Case-Control Study, Ahmet Şen, Başar Erdivanlı, Abdullah Özdemir, Hisır Kazdal, and Ersagun Tuğcugil
Volume 2014, Article ID 205164, 5 pages

Comparison of the Effect of Lidocaine Adding Dextroprofen and Paracetamol in Intravenous Regional Anesthesia, Ali Akdogan and Ahmet Eroglu
Volume 2014, Article ID 938108, 5 pages

The Effects on Sensorial Block, Motor Block, and Haemodynamics of Levobupivacaine at Different Temperatures Applied in the Subarachnoid Space, Bahittin Nazli, Huseyin Oguzalp, Eyup Horasanli, Mehmet Gamli, Beyazit Dikmen, and Nermin Gogus
Volume 2014, Article ID 132687, 7 pages

Volume 2014, Article ID 673682, 6 pages

Peri- and Postanalgesic Properties of Lidokain, Lornoxicam, and Nitroglycerine Combination at Intravenous Regional Anesthesia, Biricik Melis Cakmak, Gokhan Cakmak, Elif Akpek, Gulnaz Arslan, and Mehmet Sukru Sahin
Volume 2014, Article ID 737109, 7 pages
Pain is an outstanding problem after surgical trauma. Pain following surgery may initiate variety of mechanisms including inflammatory, visceral, or somatic in origin and may persist to be chronic pain if improperly treated. The incidence of postoperative pain has been reported to be as higher as 60%, and, despite intensive effort, it is not able to resolve completely [1].

Most of the surgeries become less invasive and are increasingly being outpatient-based in time dependent manner. Besides technical developments on surgery, this tendency is mainly dependent on effective pain control and reduction of the side effects related to the treatments. Opioids and nonsteroidal anti-inflammatory drugs are the other main components of pain therapy which have well-known side effects that may limit their use. The modern concept of pain treatment includes multimodal approach and mainly targets to decrease opioid use in combination with other drugs or techniques in order to reduce drug related side effect profile especially to prevent postoperative respiratory depression.

Until recently, there is no convincing data to demonstrate the beneficial effects of regional anesthesia on postoperative pain, opioid consumption, and related side effects such as nausea and vomiting [2].

Central neuraxial blocks alone or in combination with catheter techniques are performed in various surgical interventions in order to decrease surgically induced stress and inflammation, improve pulmonary functions, and reduce the period for ambulation with better pain control. In a meta-analysis, it has been stated that postoperative pain control with local anesthetic infusion with long term catheter placement demonstrated a decrease in the occurrence of chronic pain [3].

Peripheral nerve blocks are the other type of regional techniques. Improvement in ultrasound technology may increase clinical applications for peripheral nerve and truncal blocks. Real time ultrasound use while performing the block may reduce the complications, performance time, and local anesthetic requirements. It also provides reappraising the older techniques with carrying potential complications. The rate of success may increase with clinical experience. Peripheral nerve blocks seem to lack systemic side effect related to sympathetic blockade and lesser incidence of minor complications including urinary retention when compared with central neuraxial blocks or catheter applications. Peripheral nerve blocks seem to be safer than either central neuraxial blocks or general anesthesia, especially in patients with severe coexisting disease [2].

In this special issue, we focused on the clinical studies and review articles related to various aspects of regional
anesthesia for postoperative pain control. Some of these studies have investigated the effects of additives combined with local anesthetic mixture on postoperative analgesia in regional intravenous anesthesia. One of these reports investigated two additives, namely, ketamine or tramadol, combined with ropivacaine. While onset and duration of motor and sensory block were shorter, the period of analgesia was longer in the tramadol group in the paper entitled “Does the addition of tramadol and ketamine to ropivacaine prolong the axillary brachial plexus block?” On the same topic, the efficacy on nitroglycerine or lornoxicam combination with lidocaine for regional intravenous anesthesia was searched. Each of these drug combinations effectively increased the tolerance to the tourniquet and decreased pain during peri- and postoperative period, which is discussed in the paper entitled “Peri- and postanalgetic properties of lidokain, lornoxicam, and nitroglycerine combination at intravenous regional anesthesia.” Likewise, dexketoprofen or paracetamol combination with lidocaine was compared to each other for the same purpose. Addition of dexketoprofen increased the duration of motor block and decreased pain scores, and lesser analgesic consumptions were observed in groups with paracetamol or dexketoprofen when compared with the control, in the paper entitled “Comparison of the effect of lidocaine adding dexketoprofen and paracetamol in intravenous regional anesthesia.”

Central neuraxial blocks including spinal and epidural anesthesia were the subjects of the other studies. The effects of intraoperative intravenous magnesium sulfate infusion on sensorial and motor block characteristics and postoperative pain scales in female patients undergoing abdominal hysterectomy under spinal anesthesia were investigated. Authors indicated that the sensorial block period of spinal anesthesia increased, and better pain scores were observed with magnesium therapy without significant complications, in the paper entitled “The effect of intravenous magnesium sulfate infusion on sensory spinal block and postoperative pain score in abdominal hysterectomy.” In the other report, the difference of spinal block characteristics with levobupivacaine 0.5% plain solution at room and body temperature (23°C and 37°C) was observed in male patients undergoing transurethral resection of prostate operation. Authors indicated that the use of 0.5% levobupivacaine spinal anesthesia heated to the body temperature accelerated the start of sensory and motor block in the paper entitled “The effects on sensorial block, motor block, and haemodynamics of levobupivacaine at different temperatures applied in the subarachnoid space.”

Epidural anesthesia was the main topic for postoperative pain control in two clinical trials. The influence of preemptive local anesthetic infusion with a thoracic epidural catheter on thoracotomy was evaluated and the effects of preemptive and postoperative infusions were compared. It was shown that preemptive administration of local anesthetic solution offered superior analgesic quality and lesser analgesic consumption, which is shown in the paper entitled “The effectiveness of preemptive thoracic epidural analgesia in thoracic surgery.” In a retrospective study, the difference of analgesic efficacy of epidural anesthesia was compared with total intravenous anesthesia performed with propofol and remifentanil infusion in patients who underwent abdominal aortic aneurysm repair. It was stated that the quality of analgesia improved with epidural anesthesia, and enteral nutrition was performed earlier, in the paper entitled “Efficacy of continuous epidural analgesia versus total intravenous analgesia on postoperative pain control in endovascular abdominal aortic aneurysm repair: a retrospective case-control study.”

Caudal anesthesia is commonly performed in pediatric patients for surgical anesthesia and postoperative analgesia. In a clinical report entitled “The effects of single-dose rectal midazolam application on postoperative recovery, sedation, and analgesia in children given caudal anesthesia plus bupivacaine,” the effects of rectal midazolam combined with caudal anesthesia on the quality of sedation and postoperative analgesia were investigated, but no significant contribution was demonstrated.

Gabapentin, a drug that is used for treatment of neuropathic pain, has also been investigated for possible effects on postoperative analgesia. In a review entitled “Gabapentin in acute postoperative pain management,” the influence of gabapentin treatment on postoperative pain control was documented and it was found that gabapentin was an efficacious agent for postoperative analgesia in various types of surgery.

Pain is a common problem in all age groups of patients. Postoperative analgesia is a developing area and regional anesthesia is an essential part of this treatment. It is worthy of noting that future studies and technical developments about regional anesthesia will contribute vital advancements to postoperative pain control.

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Engin Erturk
Alparslan Apan
Urs Eichenberger
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References

Clinical Study

Does the Addition of Tramadol and Ketamine to Ropivacaine Prolong the Axillary Brachial Plexus Block?

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Background and Objectives. A prospective, randomized, controlled, double-blind clinical trial to assess the effect of tramadol and ketamine, 50 mg, added to ropivacaine in brachial plexus anesthesia. Methods. Thirty-six ASA physical statuses I and II patients, between 18 and 60 years of age, scheduled for forearm and hand surgery under axillary brachial plexus block, were allocated to 3 groups. Group R received 0.375% ropivacaine in 40 mL, group RT received 0.375% ropivacaine in 40 mL with 50 mg tramadol, and group RK received 0.375% ropivacaine in 40 mL with 50 mg ketamine for axillary brachial plexus block. The onset times and the duration of sensory and motor blocks, duration of analgesia, hemodynamic parameters, and adverse events (nausea, vomiting, and feeling uncomfortable) were recorded. Results. The onset time of sensorial block was the fastest in ropivacaine + tramadol group. Duration of sensorial and motor block was the shortest in the ropivacaine + tramadol group. Duration of analgesia was significantly longer in ropivacaine + tramadol group. Conclusion. We conclude that when added to brachial plexus analgesia at a dose of 50 mg, tramadol extends the onset and duration time of the block and improves the quality of postoperative analgesia without any side effects.

1. Introduction

Regional anesthesia provides a safe anesthesia for upper extremity surgery. Brachial plexus block with axillary approach for hand and forearm surgery is commonly used.

The use of adjuvants in combination with local anesthetics for peripheral nerve blocks enhances the quality and duration of anesthesia and postoperative analgesia. Numerous studies have been published on the effects of different adjuvants on local anesthetics for axillary brachial plexus block [1-5]. Tramadol and ketamine are the most common adjuvants used with local anesthetics [6, 7].

Tramadol is a synthetic analgesic drug that is antagonized by \( \alpha_2 \)-adrenoceptor antagonists as well as opioid antagonists [8]. Ketamine, a dissociative anesthetic N-methyl-D-aspartate (NMDA) antagonist, abolishes peripheral afferent noxious stimulation [9].

The effects of different doses of tramadol, ranging between 40 and 200 mg, and ketamine, ranging between 1 and 1.5 mg/kg, with different local anesthetics, have been reported in several studies [10-13]. However, there is no study that addresses the minimal dose required to prolong the duration of motor block, sensorial block, and analgesia without increasing adverse effects.

We designed a prospective, randomized, controlled, double-blind clinical trial to assess the effect of lower doses of tramadol and ketamine, 50 mg, added to ropivacaine in brachial plexus anesthesia to determine effectiveness of tramadol and ketamine.

2. Methods

After institutional ethics committee approval and written informed consent were obtained, 36 ASA physical statuses I and II patients, between 18 and 60 years of age, scheduled for forearm and hand surgery under axillary brachial plexus block, were included in this randomized (envelope method), controlled study. Pregnant women and patients with a history of cardiac, respiratory, hepatic, or renal failure were
excluded from the study. A 20-gauge intravenous cannula was inserted into the contralateral dorsal hand. Routine monitoring of electrocardiogram, noninvasive measurement of arterial blood pressure, peripheral oxygen saturation, and respiratory rate monitoring were conducted.

Patients were allocated to 3 groups in a controlled, randomized, double-blinded fashion. Group R received 0.375% ropivacaine in 40 mL, group RT received 0.375% ropivacaine in 40 mL with tramadol 50 mg, and group RK received 0.375% ropivacaine in 40 mL with ketamine 50 mg for axillary brachial plexus block.

Patients were premedicated with fentanyl 0.75 μg/kg and midazolam 0.03 mg/kg intravenously 10 minutes before the axillary block. Axillary block was performed in the supine position with the upper arm abducted at 90° and the elbow flexed at 90°. The area was shaved the day before and disinfected. The axillary artery was palpated in the proximal part of the axilla, and a skin wheal was injected using 1 mL of lidocaine 2%. A nerve stimulator (Stimuplex Kanüle A 50, B Braun, Melsungen, Germany) was used to identify the plexus. The position of the needle was judged adequate when an output current of less than 0.5 mA still elicited a slight distal motor response. With intermittent aspiration, the total volume was injected into the perivascular area. All the blocks were performed by the same anesthetist.

The onset times and the duration of sensory and motor blocks, duration of analgesia, hemodynamic parameters, and adverse events (nausea, vomiting, and feeling uncomfortable) were recorded. Patients were considered sedated according to Ramsay Sedation Scale ≥ 2 (Table 1).

All local anesthetic solutions and adjuvant drugs were prepared by an anesthesiologist not involved in performing brachial plexus block or data collection. All blocks were performed by one of the authors, who was unaware of the contents of the injected solution. Sensory block and motor block of musculocutaneous, radial, median, and ulnar nerves were assessed and recorded at 5-minute intervals. Sensory block of each nerve was assessed by pinprick and compared with the same stimulation of the contralateral arm as reference. Motor block was evaluated by modified Bromage scale (0 = no motion, 1 = finger movement, 2 = wrist flexion, and 3 = elbow flexion). Duration of sensory block was considered as the time interval between the local-anesthetic administration and the complete offset of anesthesia. Motor-block duration was defined as the time interval between the local-anesthetic administration and the recovery of motor function. Heart rate, peripheral oxygen saturation, respiratory rate, and blood pressure were measured before the axillary block, 5, 10, 15, 30, 45, and 60 minutes after the axillary block, and every 60 minutes thereafter for 2 hours postoperatively. Additional adverse events were recorded (bradycardia, dizziness, nausea, vomiting, and sedation).

Statistical analyses of the data were performed using t-tests and analyses of variance for parametric data to compare the differences between groups. We used Mann-Whitney U tests for nonparametric comparison of the data. A value of \( P < 0.05 \) was considered statistically significant. The results are expressed as means ± standard errors.

### 3. Results

There was no statistically significant difference between the groups in age, weight, gender, and duration of surgery (Table 2). No differences in the quality of sensory and motor blocks before and during the surgery were noted among the groups; none of the patients required supplemental analgesic during surgery. Systolic, diastolic, and mean arterial pressures were not significantly different between groups (\( P \geq 0.05 \)). Also, heart rates and oxygen saturations of all of the groups were not significantly different (\( P \geq 0.05 \)).

The distribution of the surgery types among groups is shown in Table 3, and there were no differences in the number of hand, forearm, or elbow surgeries in the groups. The onset and duration of motor block and sensorial block are shown in Table 4.

The onset time of sensorial block was the fastest in ropivacaine + tramadol group, 8.17 ± 0.33 min, compared to the ropivacaine, 9.55 ± 0.34 min (\( P = 0.015 \)), and ropivacaine+ketamine groups, 9.85 ± 0.34 min (\( P = 0.007 \)). The onset time of motor block was 10.8 ± 0.38 min, 9.3 ± 0.28 min, and 11.1 ± 0.43 min, respectively, and \( P \) values were \( P = 0.005 \) and \( P = 0.002 \).

### Table 1: Ramsay sedation scale.

<table>
<thead>
<tr>
<th>Score</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxious or restless or both</td>
</tr>
<tr>
<td>2</td>
<td>Cooperative, orientated, and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Responding to commands</td>
</tr>
<tr>
<td>4</td>
<td>Brisk response to stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Sluggish response to stimulus</td>
</tr>
<tr>
<td>6</td>
<td>No response to stimulus</td>
</tr>
</tbody>
</table>

### Table 2: Characteristics of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Group R</th>
<th>Group RT</th>
<th>Group RK</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 12 )</td>
<td>( n = 12 )</td>
<td>( n = 12 )</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>34.30 ± 4.61</td>
<td>39.8 ± 2.83</td>
<td>38.5 ± 3.72</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>10/2</td>
<td>6/6</td>
<td>12/4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 ± 1.8</td>
<td>71 ± 1.4</td>
<td>67 ± 1.0</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>73.8 ± 10.1</td>
<td>65.2 ± 13.6</td>
<td>81.7 ± 9.3</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>10/2</td>
<td>9/3</td>
<td>10/2</td>
</tr>
</tbody>
</table>

Note: values are mean ± SD.

### Table 3: Types of surgery.

<table>
<thead>
<tr>
<th>Types of surgery</th>
<th>Group R</th>
<th>Group RT</th>
<th>Group RK</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 12 )</td>
<td>( n = 12 )</td>
<td>( n = 12 )</td>
<td></td>
</tr>
<tr>
<td>Tendon reconstruction</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Contracture release</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nerve repair</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Internal fixation</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mass excision</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Duration of sensorial block was also the shortest in the ropivacaine + tramadol group, 13.16 ± 0.40 h, compared to the ropivacaine, 14.90 ± 0.33 h (P = 0.023), and ropivacaine + ketamine groups, 13.60 ± 0.30 h (P = 0.009). Duration of motor block was similar, in groups 15.8 ± 0.41 h, 13.60 ± 0.30 h, and 13.74 ± 0.33 h, respectively, and P values were P = 0.001 and P = 0.001.

Duration of analgesia was 21.6 ± 0.40 h in group R, 21.6 ± 0.40 h in group RT (P = 0.001), and 22.6 ± 0.30 h in group RK compared with group R (P = 0.08).

There was no complication during the blocking of brachial plexus blocking. We found no statistically significant differences with regard to side effects between the ropivacaine and ropivacaine + tramadol groups, but side effects were more frequently recorded in the ropivacaine and ketamine groups. Six patients in ropivacaine + ketamine group felt uncomfortable; five reported dizziness and eight reported nausea, while only two patients reported nausea in the other groups. Two patients were considered sedated in groups R and RT, but six were considered sedated in group RK (Table 5).

### Table 4: Onset and duration of anesthesia and analgesia after axillary block.

<table>
<thead>
<tr>
<th></th>
<th>Group R n = 12</th>
<th>Group RT n = 12</th>
<th>Group RK n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sensorial block (min)</td>
<td>9.55 ± 0.34</td>
<td>8.17 ± 0.33*</td>
<td>9.85 ± 0.41</td>
</tr>
<tr>
<td>Onset of motor block (min)</td>
<td>10.8 ± 0.38</td>
<td>9.3 ± 0.28*</td>
<td>11.1 ± 0.43</td>
</tr>
<tr>
<td>Duration of sensorial block (h)</td>
<td>13.6 ± 0.40</td>
<td>14.90 ± 0.33*</td>
<td>13.6 ± 0.30</td>
</tr>
<tr>
<td>Duration of motor block (h)</td>
<td>13.60 ± 0.30</td>
<td>15.8 ± 0.41*</td>
<td>13.74 ± 0.33</td>
</tr>
<tr>
<td>Duration of analgesia (h)</td>
<td>21.6 ± 0.40</td>
<td>24.90 ± 0.33*</td>
<td>22.6 ± 0.30</td>
</tr>
</tbody>
</table>

*Means P ≤ 0.05 and statistically significant.

### Table 5: Side effects between groups.

<table>
<thead>
<tr>
<th></th>
<th>Group R n = 12</th>
<th>Group RT n = 12</th>
<th>Group RK n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis</td>
<td>2</td>
<td>2</td>
<td>8*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td>6*</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Sedation</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Feeling uncomfortable</td>
<td>1</td>
<td>2</td>
<td>6*</td>
</tr>
</tbody>
</table>

*Means P ≤ 0.05 and statistically significant.

Kapral et al. assessed the use of tramadol with the 1% local anesthetic mepivacaine. They concluded that 100 mg tramadol significantly prolongs the motor and sensorial block of brachial plexus block without any side effects [14].

In a study by Sarihasan et al., use of 100 mg tramadol as an adjuvant to bupivacaine in supraclavicular plexus block improved the quality of anesthesia and extended the duration of postoperative analgesia [15].

The study of Robaux et al. also demonstrates that 40, 100, and 200 mg tramadol added to 1.5% mepivacaine for brachial plexus anesthesia extends the duration and improves the quality of postoperative analgesia in a dose dependent fashion with acceptable side effects [10]. Therefore, direct comparison of our study to these three studies is of limited value.

In some studies, 100 mg tramadol was used in different ropivacaine volumes. Kesimci et al. added 100 mg of tramadol to 40 mL of ropivacaine 7.5 mg/mL and observed a longer duration of analgesia but did not observe an improved speed of onset of block or an increase in the duration of sensory or motor block [16]. In the only study in which tramadol was added to 20 mL of 7.5 mg/mL ropivacaine, by Antonicci, it was demonstrated that tramadol significantly reduced the onset time of brachial plexus block and prolonged the duration of anesthesia and postoperative analgesia [17]. Kesimci et al. reported that the cause of the discrepancy between their findings and the findings of Antanucci may be the higher dose of (150 mg) injectate used at the same concentration of ropivacaine.

Unlike the aforementioned studies, our study used 50 mg tramadol as an adjuvant to 40 mL 0.375% ropivacaine to determine if this minimal dose of tramadol speeds the onset time of the sensorial and motor block and prolongs the duration of axillary brachial plexus block compared to ropivacaine alone. In our study addition of 50 mg tramadol supports the results of Antonicci rather than Kesimci with longer duration of analgesia only without prolonging onset and the duration of sensory or motor block. However, direct comparison to our study is of limited value because different local anesthetics with different volumes and concentrations were used.

Ketamine was another adjuvant used in this study that was reported as an effective agent with local anesthetics. The contributory effect of the addition of ketamine, an N-methyl-D-aspartate (NMDA) antagonist, was evaluated when the drug is delivered via caudal [6, 8], epidural [18, 19], and spinal [20, 21] routes. In all these studies, addition of ketamine with antagonism to NMDA receptors and

### 4. Discussion

The results of this study suggest that the addition of 50 mg tramadol to 0.375% ropivacaine for axillary brachial plexus block prolongs the duration of anesthesia and analgesia without increasing side effects, whereas addition of 50 mg ketamine to 0.375% ropivacaine does not provide any additional effect.

There are few studies about the addition of tramadol to local anesthetics in axillary brachial plexus block. Most published experience has been obtained with the dose of 100 mg of tramadol with different local anesthetics.
an axonal conduction block may also contribute to the analgesic mechanism of regional ketamine to different local anesthetics which provided a success on both block duration and quality. Senel et al. reported that 50 mg ketamine, as an adjuvant to local anesthetic, is an effective dose in spinal anesthesia. In the study of Lee et al., the addition of 30 mg ketamine in a volume of 30 mL ropivacaine 0.5% did not improve the onset and duration of brachial plexus block because of a low dose of ketamine; however, there was a relatively high incidence of adverse effects [22].

In our study, addition of 50 mg ketamine to 0.375% ropivacaine did not provide any additional effect on axillary brachial plexus. The possible cause of this may be the low concentration of 50 mg ketamine in a volume of 40 mL. In our opinion, a higher concentration of ketamine is necessary for ketamine to be used as an adjuvant to local anesthetics in brachial plexus block. However, using a higher concentration means more ketamine-induced adverse effects.

Few studies report adverse effects when various doses of tramadol and ketamine are added to local anesthetics as adjuvants. These studies found no difference in adverse effects when comparing the ropivacaine alone group to a group in which 100 mg tramadol was added for brachial plexus. Our study confirmed these results [23–25].

We found no statistically significant differences with regard to the side effects between the groups R and RT, but all side effects in the RK group, except dizziness and sedation, were significantly different.

Nausea and vomiting were observed in the RK group, possibly due to the emetic effect of ketamine that is caused by release of endogenous catecholamine. Feelings of discomfort are also known effects of ketamine.

We conclude that when added to brachial plexus analgesia at a dose of 50 mg, tramadol extends the onset and duration time of the block and improves the quality of postoperative analgesia without any side effects. Further studies of the effects of lower doses of tramadol with various combinations of tramadol and local anesthetics are needed, before final recommendations can be made.

Our findings do not encourage the use of ketamine for brachial plexus block. Ketamine does not enhance the local anesthetic effect at the level of the axillary brachial plexus nerve roots and does not prolong postoperative analgesia with the dose of 50 mg when combined with ropivacaine. In addition, the high incidence of ketamine-induced adverse effects at this dose is disturbing.

These findings make us ask the question of “do we need to use ketamine as an adjuvant to local anesthetics in brachial plexus blockage?”

The answer is that we have more than one alternative.

Disclosure
This paper has not been published elsewhere in whole or in part in any congress or any journal.

Conflict of Interests
The authors have no conflict of interests to declare.

References


Gabapentin in Acute Postoperative Pain Management

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Gabapentin (1-aminomethyl-cyclohexaneacetic acid) is an amino acid that has the structure of the neurotransmitter \( \gamma \)-aminobutyric acid (GABA). It is a novel drug used for the treatment of postoperative pain with antihyperalgesic properties and a unique mechanism of action. Gabapentin and the related, more potent compound pregabalin have been shown to be beneficial in the treatment of neuropathic pain as well as postoperative pain following spinal surgery and hysterectomy. This study reviews five aspects of gabapentin: (1) chemical and structural characteristics; (2) pharmacokinetics and pharmacodynamics; (3) application in acute pain management; (4) adverse effects; and (5) drug safety. Overall, gabapentin has been reported to be a safe and efficacious drug for the treatment of postoperative pain.

1. Introduction

Primarily, three different classes of drugs are utilized for the treatment of postoperative pain (anti-inflammatories, local anesthetics, and opioids). Unfortunately long-term clinical use of these agents is limited by their side effects. Gabapentin is a novel drug used for the treatment of postoperative pain with antihyperalgesic properties and a unique mechanism of action, which differentiates it from other commonly used drugs. Various studies have shown that perioperative use of gabapentin reduces postoperative pain.

Gabapentin works by reducing lesion-induced hyperexcitability of posterior horn neurons, which is responsible for central sensitization [1]. The mechanism of the antihyperalgesic action may be a result of the postsynaptic binding of gabapentin to the \( \alpha_2 \delta \) subunit of the dorsal horn neurons’ voltage-dependent calcium channels, causing decreased calcium entry into nerve endings and thus decreased release of neurotransmitters. Other possible cellular mechanisms include the effects of gabapentin on NMDA receptors, sodium channels, monoaminergic pathways, and the opioid system [2–5].

Gabapentin was initially introduced in 1994 as an antiepileptic drug (AED), primarily for partial seizures. It is an anticonvulsant whose side effects are well tolerated and well absorbed after oral administration with the maximal plasma concentration seen after two to three hours [2, 6]. Some of the most commonly reported side effects of gabapentin include dizziness, somnolence, fatigue, ataxia, and peripheral edema [4, 7].

Gabapentin has also been found to be beneficial in treating neuropathic pain related to postherpetic neuralgia (PHN) [8, 9], postpoliomyelitis neuropathy [10], and reflex sympathetic dystrophy [11]. Additionally, gabapentin has been shown to play a role in treating pain related to diabetic neuropathy [12] in placebo-controlled clinical trials.

This study reviews five aspects of gabapentin: (1) chemical and structural characteristics; (2) pharmacokinetics and pharmacodynamics; (3) application in acute pain management; (4) adverse effects; and (5) drug safety.

2. Chemical and Structural Characteristics

Gabapentin [1-(aminomethyl)cyclohexaneacetic acid] is a structural analog of the inhibitory neurotransmitter \( \gamma \)-aminobutyric acid (GABA) [13]. It is a white to off-white crystalline solid substance with the molecular formula, \( \text{C}_9\text{H}_{17}\text{NO}_2 \), and a molecular weight of 171.237 g/mol. Freely soluble in water and in both basic and acidic aqueous solutions, gabapentin is highly charged at physiological pH and exists as a zwitterion with a \( pK_{a1} \) of 3.68 and \( pK_{a2} \) of 10.70...
Gabapentin is assayed in plasma and urine using gas chromatography [15], high performance liquid chromatography [16], and high performance liquid chromatography with UV-vis detection [17].

3. Pharmacodynamics

Though it is structurally similar to GABA, gabapentin does not bind to GABA_A or GABA_B receptors, does not block GABA uptake or metabolism, and has no direct GABAergic action [18]. The mechanism of action of gabapentin is different from that of several drugs that interact with GABA synapses such as valproate, barbiturates, and benzodiazepines; it is thought to exert its action by interaction with a receptor associated with the L-system amino acid carrier protein. In vitro studies with radiolabelled gabapentin have shown that gabapentin binds preferentially to neurons in the outer layer of the rat cortex and the hippocampus at sites distinct from other anticonvulsants [19]. Because the maximal anticonvulsant effect is seen 2 hours after an intravenous injection in rats, it is probable that gabapentin exerts its action at an intracellular site [20].

Gabapentin inhibits the tonic phase of nociception stimulated by formalin and carrageenan and in neuropathic pain models prevents mechanical and thermal allodynia and mechanical hyperalgesia [18]. Though the mechanism of action of gabapentin in the treatment of neuropathic pain is not clear, it does not influence the same pathways as opioids or tricyclic depressants. Current evidence indicates that gabapentin affects voltage-gated calcium channels in the CNS.

Gabapentin binds to the α_2δ subunit of the voltage-dependent calcium channel, regulating the action of the calcium channels and neurotransmitter release [15, 21, 22]. It is suggested that the antihyperalgesic action of gabapentin is due to its binding to this site on the voltage-gated calcium channel. Fink et al. demonstrated that gabapentin blocks neuronal calcium influx in a concentration-dependent manner by inhibiting P/Q-type calcium channels in the rat neocortex [23]. Decreased AMPA receptor activation and norepinephrine release in the brain are observed due to the reduced calcium influx, which decreases excitatory amino acid (glutamate) release [24]. These results support the hypothesis that the analgesic effects of gabapentin in neuropathic pain are mediated by the inhibition of voltage-gated calcium channels.

Other effects of gabapentin that do not have major pharmacodynamic significance include slight reductions in the release of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) from mammalian brain tissue [25, 26] and a decrease in sodium-dependent action potentials, indicating sodium channel blockade, after prolonged exposure [27].

4. Pharmacokinetics

Administered orally, gabapentin is absorbed in part by diffusion and in part by the carrier-mediated, L-amino acid transport system [28]. As a result of the saturable transport mechanism, the bioavailability of gabapentin is inversely dependent on the dose [29]. It ranges from approximately 60% for a 300 mg dose [30] to 40% for a 600 mg dose [31] and 35% at steady state with doses of 1600 mg three times daily [32]. The bioavailability of gabapentin is not affected by the presence of food and remains unchanged following multiple dose administration. Mean maximum plasma gabapentin concentrations (C_max) of 2.7 ± 2.99 mg per liter are reached in healthy volunteers approximately 3 hours after a single oral 300 mg dose [30, 33]. When the dose is tripled from 300 mg to 900 mg, C_max increases less than threefold due to the dose dependent saturable absorption of gabapentin [32].

Gabapentin has a high volume of distribution of 0.6–0.8 L/kg or 50–60 L in healthy volunteers [30, 32, 33] and does not bind to human plasma proteins [34]. Unlike GABA, gabapentin readily penetrates the blood-brain barrier, yielding CSF concentrations equal to 20% of plasma concentrations and estimated between 0.09 and 0.14 µg per mL [33, 35]. Brain tissue concentrations are 80% of corresponding plasma levels [36]. In rats, gabapentin concentrates in the pancreas and kidneys. Pancreatic and renal tissue concentrations are eight and four times higher than serum concentrations, respectively [37]. The drug does not accumulate in the pancreas in humans since it exists in a highly ionized state at physiological pH and concentrations in adipose tissue are low [37].

In contrast to many antiepileptic drugs, which are metabolized, gabapentin is not metabolized in humans and is eliminated solely by renal clearance. The drug is excreted unchanged in urine and undergoes first order kinetic elimination [29, 33]. Plasma clearance of gabapentin is directly proportional to creatinine clearance; consequently, renal impairment reduces gabapentin excretion and increases plasma gabapentin concentrations in a linear fashion [33, 34, 37, 38]. Patients with renal failure should receive their maintenance dose of gabapentin after each treatment as gabapentin is removed during hemodialysis [39]. Although a dose response pattern is apparent for plasma gabapentin concentrations and for clinical effect for doses ranging from 600 to 1800 mg per day, it is not necessary to monitor plasma gabapentin concentrations and gabapentin dose should be modified based on clinical response [33]. The elimination half-life of gabapentin is between 5 and 9 hours, and as a result, three divided doses are usually required per day, but steady state is rapidly achieved [29].

Gabapentin is unique among anticonvulsant drugs as it lacks hepatic metabolism, exhibits low protein binding, and does not induce or inhibit hepatic microsomal enzymes or inhibit the metabolism of other antiepileptic drugs [29, 34]. No significant pharmacokinetic interactions have been reported between gabapentin and conventional antiepileptic drugs (valproic acid, phenobarbital, carbamazepine, or phenytoin) or oral contraceptives [29, 34]. However, cimetidine, which decreases glomerular filtration rate, reduces the clearance of gabapentin by 12% [32]. In addition, the bioavailability of gabapentin is decreased by 20% by antacids when taken simultaneously or up to 2 hours after gabapentin administration [40].
5. Application in Acute Pain Management

5.1. Coronary Artery Bypass Graft. Ucak et al. evaluated the analgesic effects of perioperative gabapentin after coronary artery bypass graft (CABG) surgery with median sternotomy as well as internal mammary artery harvesting [41]. They used a gabapentin dose of 1.2 g per day treatment 1 hour before surgery and for 2 days after surgery and investigated its effect on postoperative acute pain. In this study, postoperative pain scores at 1, 2, and 3 days as well as the consumption of tramadol which was given as rescue analgesic were significantly lower in the gabapentin group when compared to the placebo group [41].

5.2. Thoracic Surgery. Zakkar et al. performed a literature search and identified five papers with the best evidence regarding the use of gabapentin to reduce the incidence of pain experienced by patients after thoracic surgery [42–46]. They concluded that there is no evidence to support the role of a single preoperative oral dose of gabapentin in reducing pain scores or opioid consumption after thoracic surgery. Furthermore, more robust randomized control studies are needed to validate the efficacy of multiple dosing regimens but studies currently show that it may be beneficial in reducing acute pain [42].

5.3. Thyroid Surgery. Lee et al. explored the efficacy of using gabapentin (600 mg) 1 hour before the administration of anesthesia for thyroid surgery [47]. He determined that the gabapentin group had a lower incidence of postoperative sore throat (POST) and a significantly lower visual analogue scale (VAS) score at 6 and 24 hours at rest after the completion of the surgery compared to the placebo group. However, there was no intergroup difference between the gabapentin group and the placebo group in terms of the incidence of POST or VAS score during the swallowing movement. From this study they were able to conclude that the gabapentin administered 1 hour prior to anesthesia decreased the intensity and incidence of POST at rest without a significant adverse event within the first 24 hours after thyroid surgery but not during the swallowing movement [47].

5.4. Neurological Surgery. Misra et al. performed a study to investigate patients undergoing craniotomies and the efficacy of gabapentin plus dexamethasone on postoperative nausea and vomiting (PONV) and pain after craniotomy [48]. Patients undergoing craniotomy received gabapentin (600 mg) premedication orally 2 hours prior to induction of anesthesia as well as 4 mg of intravenous dexamethasone on the morning of surgery and continued receiving it after every 8 hours. The 24-hour incidence of nausea, emesis, or PONV and postoperative pain scores were evaluated. This study observed a significant difference between the group that received gabapentin and dexamethasone and the placebo group in the incidence of nausea and the requirements for antiemetics. However, there was no significant difference in either the postoperative pain scores or the opioid consumption between the gabapentin with dexamethasone cohort and the placebo cohort. Therefore, although there was no reduction in either the postoperative pain scores or opioid consumption, gabapentin plus dexamethasone significantly reduced the 24-hour incidence of nausea and PONV [48].

5.5. Lumbar Spinal Surgery. Yu et al. performed a systematic review and meta-analysis to determine the efficacy of gabapentin in the management of postoperative pain after lumbar spinal surgery. They showed that oral gabapentin was efficacious in the management of postoperative pain at every time point during the first day after surgery and therefore is efficacious in reducing postoperative pain and narcotic requirements after lumbar spinal surgery [49].

5.6. Hysterectomy. Ajori et al. performed a study investigating the preemptive use of gabapentin (600 mg) prior to abdominal hysterectomy and its influence on nausea and vomiting, and meperidine consumption [50]. Pain was assessed on a visual analogue scale (VAS) at 1, 4, 6, 12, and 24 hours postsurgically. This study showed that gabapentin group had significantly lower VAS scores at every time interval compared to the placebo group and the total meperidine consumed in the gabapentin group was significantly less than in the placebo group. PONV and the consumption of antiemetic drugs were also significantly reduced in the gabapentin group. Therefore, preemptive use of 600 mg gabapentin orally in patients undergoing abdominal hysterectomies significantly decreases postoperative pain and PONV and also reduces analgesic and antiemetic drug requirements [50].

5.7. Major Bowel Surgery. Siddiqui et al. performed a study investigating the effects of gabapentin (600 mg) orally 1 hour prior to surgery in patients with inflammatory bowel disease (IBD) undergoing major bowel surgery. This group found that a single preoperative administration of 600 mg gabapentin in patients undergoing major bowel surgery does not reduce postoperative pain scores, opioid consumption, or opioid-related side effects [51].

5.8. Orthopedic Surgery. Panah Khahi et al. explored the efficacy of preemptive use of gabapentin on reduction of postoperative pain in the first 24 hours after internal fixation of the tibia under spinal anesthesia [52]. Patients were administered 300 mg of gabapentin two hours before surgery and postoperative pain was evaluated using VAS two, 12 and 24 hours after surgery. The time from the completion of the surgery until the first bolus dose of morphine on demand and the total morphine required were also evaluated. This study showed that the pain score was significantly lower in the gabapentin group compared to the placebo group two hours after the completion of the surgery; however, the scores 12 and 24 hours after surgery were not significantly different between the two groups. Therefore, preemptive use of gabapentin 300 mg orally significantly alleviated postoperative pain two hours after internal fixation of the tibia [52].
6. Adverse Effects

Gabapentin may have dose-limiting side effects, which could prevent some patients from achieving therapeutic plasma levels. Studies have reported no significant difference in the frequency of adverse events in patients receiving a higher dose as compared to those receiving a lower dose of gabapentin [53]. The most consistently cited adverse effects of gabapentin are somnolence and dizziness. While these side effects are considered to be minor, they may be worrisome in the elderly population, which is prone to injuries from falls and gait instability. Given this issue, clinicians may opt to discontinue gabapentin in clinical practice in this age group [54]. One possible explanation for these side effects is the multiple peaks and troughs in plasma concentration levels observed with treatment regimens consisting of multiple doses per day [54]. Since many clinical trials have shown that gabapentin demonstrates improvement in sleep, there may be an advantage for a formulation of gabapentin that peaks during the night, with lower levels during the day.

Clivatti et al. performed a study looking at twenty-six randomized, placebo-controlled, clinical studies between 2005 and 2007 and evaluated the effects of gabapentin preoperatively (PRE Group) and pre- and postoperatively (PRE-POST Group) [55]. The study reported adverse effects which included postoperative nausea and vomiting, sedation, and dizziness. In the PRE Group, which consisted of seventeen studies, a reduction in the incidence of nausea and vomiting in patients treated with gabapentin was observed in two studies while an increase in nausea and vomiting was reported in one study. Additionally, a higher incidence of sedation was reported in one study while a higher incidence of dizziness was seen in another study. In the PRE-POST Group, which consisted of nine studies, one study reported an increase in the incidence of postoperative nausea and vomiting, another study reported an increase in sedation, and two studies reported an increase in the incidence of dizziness [55]. Likewise, a study by Fassoulaki et al. did not observe intolerable side effects with the use of gabapentin for the daily dose of 1600 mg/d. Some sedation was exhibited by their patients, especially in the beginning of treatment, but that is desirable before and immediately after surgery.

Turan et al. investigated the effects of gabapentin on acute postoperative pain and on morphine consumption in patients undergoing spinal surgery where 1,200 mg gabapentin was given 1 hour before surgery. The most common adverse effects of gabapentin observed during the study were dizziness and nausea but the number of incidences did not significantly differ from the placebo group and therefore no significant adverse effects were associated with a single oral dose of gabapentin [56]. However, in that same study, there was a significant decrease in vomiting and urinary retention in the gabapentin group versus the placebo group; therefore gabapentin decreased the side effects associated with morphine in patients undergoing spinal surgery [56].

Sen et al. showed that although the most common side effects after an elective hysterectomy were nausea and vomiting, there were no differences in the incidence of these side effects between the perioperative administration of a placebo, ketamine, and gabapentin [57]. Similarly, Gilron et al. assessed the efficacy and tolerability of gabapentin, nortriptyline, or a combination of both which showed that both during dose titration and at the maximum tolerated dose, the most common adverse event was moderate or severe dry mouth, which occurred significantly less frequently in patients on gabapentin than on nortriptyline or combination treatment [58]. There were no other significant differences in adverse events [58].

Furthermore, a study by Compton et al. evaluated the efficacy of gabapentin, a key agent for neuropathic pain, to reverse opioid-induced hyperalgia in methadone maintenance for the treatment of addiction patients [59]. The two most commonly reported adverse events in this study were nausea and dizziness/light-headedness which were both reported to be greater in the gabapentin group than in the placebo group [59].

A major complication that develops after the abrupt discontinuation of high-dose gabapentin used for the prevention of chronic postsurgical pain is withdrawal symptoms that clinically resemble alcohol or benzodiazepine withdrawal [60]. Signs and symptoms include irritability, agitation, anxiety, palpitation, and diaphoresis within 1-2 days. Secondary to gabapentin withdrawal, a patient with chronic back pain also developed generalized seizures and status epilepticus [61]. Tapering should always be performed especially in patients taking higher doses; however, withdrawal syndrome can still rarely be observed despite dose tapering [62].

7. Pharmacovigilance

Gabapentin has been reported to be a well-tolerated and safe drug [12, 33, 63]. Studies on safety issues have reported adverse effects including dizziness, somnolence, confusion, headache, nausea, ataxia, and weight gain [53, 64]. However, these side effects were usually reported after long-term gabapentin use and usually diminish with time but may be bothersome in an acute setting to a postoperative patient. Studies which reported these side effects used the drug for 8 weeks to doses titrated up to 3600 mg per day, unless severe adverse effects were developed.

Rowbotham et al. conducted a randomized controlled trial to determine the safety of gabapentin in reducing postherpetic neuralgia [63]. In this study, they used 229 subjects and performed a 4-week titration period to maximum dose of 2600 mg per day of gabapentin or matching placebo. The treatment was maintained for another 4 weeks at the maximum tolerated dose. They found that minor adverse events that were determined to be associated with the study medication were reported in 62 subjects receiving gabapentin and 32 subjects receiving placebo. The investigator reported no serious adverse events that were related to gabapentin. In this study, the most frequently reported adverse effects within the gabapentin group which were greater than the placebo group were somnolence (27.4% versus 5.2%), dizziness (23.9% versus 5.2%), ataxia (7.1% versus 0.0%), peripheral edema (9.7% versus 3.4%), and infection (8.0% versus 2.6%) [63].

McLean et al. performed a study which evaluated and demonstrated the tolerability and safety of gabapentin when
used as an adjunctive therapy in doses required to achieve the most effective seizure control in patients with epilepsy [53]. This study compared tolerability of gabapentin dosages less than or equal to 1,800 mg versus those greater than 1,800 mg per day. The safety analysis required patients to be followed up after receiving at least one dose of gabapentin and included 2,216 patients [53]. The safety of gabapentin therapy was evaluated by the following parameters: (1) adverse event reports, (2) physicians’ assessment of safety and tolerability at study completion or termination, (3) neurologic examinations at baseline and study completion or termination, and (4) vital signs (sitting systolic and diastolic blood pressure, sitting heart rate) which were taken at baseline and study completion or termination. An adverse event was defined as a noxious or unintended event observed in or reported by a patient who was participating in the study and had received study medication and these adverse events were further classified relative to gabapentin therapy as definitely, probably, possibly, unlikely/remote, or definitely not related. An associated adverse event was defined as an event that was considered by the investigator to be definitely, probably, or possibly related to treatment with gabapentin.

In this study, McLean et al. showed that 48.3% of patients reported the occurrence of at least one adverse event and 36.4% of patients reported at least one associated adverse event [53]. The most common adverse events for patients receiving less than or equal to 1,800 mg/day were asthenia, headache, dizziness, and somnolence while the most common adverse events for patients receiving greater than 1,800 mg/day were somnolence, dizziness, and weight gain. No adverse events were reported to occur at a significantly higher percentage of patients while receiving the higher dose compared to the lower dose of gabapentin. The rate of withdrawal from the study did not increase at higher doses suggesting that the incidence of adverse events does not increase at higher doses or longer use of gabapentin [53].

A serious adverse event was defined as any event that was fatal, life-threatening, and permanently disabling, required or prolonged inpatient hospitalization, or was a congenital anomaly, cancer, or overdose and was reported in only 3.3% of patients [53]. The most common serious adverse event was convulsion, reported by 0.9% of patients [53]. Eleven (0.4%) patients died during the study although no deaths were considered to be associated with gabapentin treatment [53]. The safety and tolerability of gabapentin as determined by the physicians at the completion of the study or dropout were judged to be good or excellent for 78.5% of patients. Additionally, the treatment of gabapentin did not adversely affect vital signs in this study [53]. Overall, gabapentin was determined to be safe and doses greater than 1,800 mg/day were well tolerated and not associated with more adverse events.

Backonja et al. investigated the effect of gabapentin monotherapy on pain associated with diabetic peripheral neuropathy by titrating from 900 to 3600 mg per day or maximum tolerated dosage or placebo [12]. The safety of gabapentin was determined by using adverse event data (occurrence, intensity, and relationship to gabapentin) and the results of physical and neurological examination, including peripheral sensory examinations. During this study a total of seven gabapentin-treated patients (8%) withdrew from the study due to adverse events which included dizziness and somnolence, abdominal pain, asthenia, body odor, headache, diarrhea, abnormal thinking, nausea, confusion, and hypesthesia. Out of the placebo group, only 5 patients (6%) withdrew due to dyspepsia, constipation, flatulence infection, and somnolence. Most adverse events in patients treated with gabapentin were described as mild or moderate intensity. There were no significant changes in hemoglobin A1C levels from baseline to the termination of treatment in either group. As such, glycemic control was maintained during the study. Neurological examination data revealed no significant differences in the rate of disease progression and the proportion of patients with a change from normal or decreased at baseline to absent at study termination was similar between groups (less than 14% in each case) for the 3 sensory modalities tested (temperature, light touch, and pin prick). Dizziness and somnolence were the two adverse events reported to occur more frequently in the gabapentin group. Overall, this study showed that gabapentin monotherapy produced rapid onset of clinical meaningful pain relief with relatively minor and potentially avoidable adverse effects; in turn, this further supports the safety of gabapentin as described in the prior studies [12].

8. Conclusion

Clinical studies have shown that gabapentin can reduce acute postoperative pain, decreasing the need for opioids. For example, a gabapentin dose of 1.2 grams per day 1 hour before surgery and for 2 days after CABG surgery showed that postoperative pain scores at 1, 2, and 3 days as well as the consumption of tramadol given as a rescue analgesic were significantly lower in the gabapentin group when compared to the placebo group [41]. Additionally, preemptive use of gabapentin 300 mg orally significantly alleviated postoperative pain two hours after internal fixation of the tibia. Similarly, preemptive use of 600 mg gabapentin orally in patients undergoing abdominal hysterectomies significantly decreases postoperative pain and PONV and also reduces analgesic and antiemetic drug requirements [50]. While some studies suggest that gabapentin does not significantly reduce postoperative pain scores or opioid consumption, it has been shown to significantly reduce the 24-hour incidence of nausea and PONV. Overall, gabapentin has been reported to be a well-tolerated, safe, and efficacious drug.

Conflict of Interests

The authors declare that they have no conflict of interests.

References


Clinical Study

Efficacy of Continuous Epidural Analgesia versus Total Intravenous Analgesia on Postoperative Pain Control in Endovascular Abdominal Aortic Aneurysm Repair: A Retrospective Case-Control Study

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We reviewed our experience to compare the effectiveness of epidural analgesia and total intravenous analgesia on postoperative pain control in patients undergoing endovascular abdominal aortic aneurysm repair. Records of 32 patients during a 2-year period were retrospectively investigated. TIVA group (n = 18) received total intravenous anesthesia, and EA group (n = 14) received epidural anesthesia and sedation. Pain assessment was performed on all patients on a daily basis during rest and activity on postoperative days until discharge from ward using the numeric rating scale. Data for demographic variables, required anesthetic level, perioperative hemodynamic variables, postoperative pain, and morbidities were recorded. There were no relevant differences concerning hospital stay (TIVA group: 14.1 ± 7.0, EA group: 13.5 ± 7.1), perioperative blood pressure variability (TIVA group: 15.6 ± 18.1, EA group: 14.8 ± 11.5), and perioperative hemodynamic complication rate (TIVA group: 17%, EA group: 14%). Postoperative pain scores differed significantly (TIVA group: 5.4 ± 0.9, EA group: 1.8 ± 0.8, \( P < 0.001 \)). Epidural anesthesia and postoperative epidural analgesia better reduce postoperative pain better compared with general anesthesia and systemic analgesia, with similar effects on hemodynamic status.

1. Introduction

Abdominal aortic aneurysm is common in men older than 65 years of age. Most of these patients have a history of chronic tobacco smoking, chronic obstructive pulmonary disease, hypertension, and hyperlipidaemia [1]. Smoking and pulmonary disease may cause postoperative respiratory failure following general anesthesia due to increased atelectasis [2]. Inadequate postoperative analgesia may also promote atelectasis formation due to the patient’s inability to cough. Conversely, use of rescue analgesics may cause hemodynamic fluctuations in such hypertensive patients and precipitate hemorrhagic or ischemic complications. Epidural analgesia is shown to improve hemodynamic stability and postoperative analgesia, alone [3] or combined with general anesthesia [4] in major abdominal surgery. We reviewed endovascular abdominal aortic aneurysm repair (EVAR) cases over a 2-year period and compared epidural anesthesia with general anesthesia in terms of perioperative hemodynamic stability and postoperative analgesia.

2. Materials and Methods

Following approval by the local ethics committee, we retrospectively investigated records of patients who had undergone EVAR surgery during the period from October, 2011, to October, 2013, in our institution. Patients, who received spinal anesthesia and combined regional and general anesthesia were excluded. One patient, who was operated with general anesthesia for 490 minutes due to accidental vascular tear, massive blood loss, and cardiac arrest during operation, was also excluded.
2.1. Data Collection. Two anesthesiologists reviewed the charts of all eligible patients. The following data were obtained: (1) demographic variables and medical history (age, gender, American Society of Anesthesiologists (ASA) risk score, and comorbidities) and cardiovascular events such as arrhythmia and treatments, baseline resting blood pressure, and heart rate were obtained from ward charts; (2) anesthesia method, drug, doses, recordings of continuous electrocardiographic, pulse oximetry, urine output, central venous pressure (via internal jugular or subclavian vein catheterization), invasive blood pressure monitoring (via radial artery cannulation), intraoperative fluid therapy, urine output, blood loss and transfusion, hemodynamic events, and treatments were obtained from anesthesia charts; (3) blood pressure, heart rate, fluid therapy, urine output, postoperative pain (pain assessment was performed on all patients on a daily basis during rest and activity until discharge from the intensive care unit (ICU) using the numeric rating scale (as described in Table 1) [5]), analgesic requirement, and morbidities were obtained from the ICU chart.

2.2. Statistics. Normality of distributions was tested with Shapiro-Wilk test. Parametric data were presented as mean ± standard deviation (SD), nonparametric data were presented as median ± SD, and categorical data were presented as number (%). Parametric data (age, hospital stay, nutrition and fluid intake, and duration of postoperative active warming) were analyzed with student t-test, nonparametric data (operation duration, blood pressure values, heart rate values, intravenous fluids, urine output, occurrence of hemodynamic complications, and pain scores) were analyzed with Mann-Whitney U test, and categorical data (gender and ASA scores) were analyzed with chi-square test. The relationship between continuous variables such as intravenous fluids or urine output and duration of operation was analyzed with analysis of variance (ANOVA); a P < 0.05 was considered statistically significant.

3. Results

Data from a total of 31 (27 males and 4 females) patients were analyzed. We found that 17 patients (TIVA group) received total intravenous anesthesia (TIVA) and 14 patients (EA group) received epidural anesthesia. Patients' demographic data were summarized in Table 2. There were no statistically significant differences between patients receiving either form of anesthesia in terms of gender, age, and comorbidities. Hospital stay did not differ significantly between TIVA group (14.1 ± 7.0 days) and EA group (13.5 ± 7.1 days).

3.1. Anesthesia Method. It is understood that, following an intravenous (iv) bolus of 3 mg midazolam, epidural catheterization was performed at sitting position, at the L2-3 interspace, with an initial bolus of 20 mL of epidural 0.25% bupivacaine and continuous infusion of epidural 0.125% bupivacaine at a rate of 5 mL/h.

Anesthesia chart review revealed that, following an iv bolus of 2 mg of midazolam, TIVA was induced with a mean of 2.3 ± 0.1 mg/kg iv propofol and a mean of 2.2 ± 0.2 mcg/kg iv fentanyl. Neuromuscular block was induced with 0.6 mg/kg iv rocuronium and was maintained with regular bolus doses of 0.15 mg/kg iv every 30 minutes, except one patient, who required an additional dose every 15 minutes. According to anesthesia charts, anesthesia was maintained with 90–160 mcg/kg/min iv propofol infusion and 0.02–0.2 mcg/kg/min iv remifentanil infusion. Propofol infusion rate was adjusted to obtain a bispectral index value of 40–60. The mean bispectral index value obtained from the anesthesia charts was 43.9 ± 2.8. Remifentanil infusion rate was adjusted when blood pressure or heart rate varied.

3.2. Preoperative Hemodynamic Variables. Ward chart review for preoperative blood pressure and heart rate showed that 11 patients (4 in TIVA group and 7 in EA group) were hypertensive during the preoperative course, and 9 patients (4 in TIVA group, 5 in EA group) had a short course of supraventricular tachycardia, which required initiation of amiodarone therapy.

3.3. Preoperative Nutrition and Fluid Intake. Ward chart review for preoperative nutrition and fluid intake showed that 5 patients (15.6%), who had signs of pneumonia, received additional enteral nutrition (mean of 11.4 ± 1.2 kcal/kg/day). No patient received any form of parenteral nutrition. Urine output was not recorded during preoperative period.

3.4. Intraoperative Hemodynamic Variables. Intraoperative hemodynamic variables are summarized in Table 3. Anesthesia chart review showed that mean blood pressure dropped by a mean of 15.3 ± 15.3%. Drop in mean blood pressure was as high as 37–50% in 3 patients in TIVA group and in 2 patients in EA group. These patients required administration of iv ephedrine in addition to iv colloids. There was no occurrence of hypertensive, tachycardic, or bradycardic episode.

3.5. Intraoperative Fluid Intake and Urine Output. Regardless of the anesthesia method used, all patients received a median of 1125 ± 565 mL iv fluid during the operation according to the anesthesia chart (P = 0.9). Anesthesia charts showed that fluid loss during the preoperative fasting period was calculated according to patient’s body weight. Patients received half of this volume during the first hour of surgery and the other half during the next two hours. Therefore, iv fluid administered during the operation was directly proportional to the duration of the operation, as analyzed by ANOVA.

### Table 1: Numeric rating scale.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Pain level</th>
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<tbody>
<tr>
<td>0</td>
<td>No pain</td>
</tr>
<tr>
<td>1–3</td>
<td>Mild pain (nagging, annoying, and interfering a little with daily activities)</td>
</tr>
<tr>
<td>4–6</td>
<td>Moderate pain (interferes significantly with daily activities)</td>
</tr>
<tr>
<td>7–10</td>
<td>Severe pain (disabling)</td>
</tr>
</tbody>
</table>
Table 2: Patient demographics obtained from patient charts. Data are represented as mean ± SD, number, or number (percent).

<table>
<thead>
<tr>
<th></th>
<th>TIVA (n = 17)</th>
<th>Epidural anesthesia (n = 14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71 ± 7.5</td>
<td>75.8 ± 6.4</td>
<td>NA</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>15/2</td>
<td>12/2</td>
<td>NA</td>
</tr>
<tr>
<td>ASA score (II/III/IV)</td>
<td>1/15/0</td>
<td>6/8/1</td>
<td>NA</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (88%)</td>
<td>13 (93%)</td>
<td>NA</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>15 (88%)</td>
<td>13 (93%)</td>
<td>NA</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13 (76%)</td>
<td>3 (21%)</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (23%)</td>
<td>3 (21%)</td>
<td>NA</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>9 (53%)</td>
<td>12 (86%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Duration of operation, hemodynamic variables, and complications recorded during the operations. Data are represented as median ± SD or number (percent).

<table>
<thead>
<tr>
<th></th>
<th>TIVA (n = 17)</th>
<th>Epidural anesthesia (n = 14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of operation (min)</td>
<td>140 ± 44</td>
<td>125 ± 31</td>
<td>NA</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>83 ± 13</td>
<td>80 ± 15</td>
<td>NA</td>
</tr>
<tr>
<td>Mean heart rate (beats/min)</td>
<td>80 ± 14</td>
<td>80 ± 10</td>
<td>NA</td>
</tr>
<tr>
<td>Median intravenous fluid (mL)</td>
<td>1250 ± 615</td>
<td>875 ± 485</td>
<td>NA</td>
</tr>
<tr>
<td>Mean urine output (mL)</td>
<td>350 ± 50</td>
<td>400 ± 60</td>
<td>NA</td>
</tr>
<tr>
<td>Median red blood cells transfused (units)</td>
<td>0 ± 2</td>
<td>0 ± 0</td>
<td>NA</td>
</tr>
<tr>
<td>Number of hypotensive episodes</td>
<td>3 (17%)</td>
<td>2 (14%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

(P < 0.0001). All patients received 500 mL of iv colloid, and the rest of iv fluids were isotonic sodium chloride 0.9%. Hourly urine output results during surgery showed that all patients had 1 mL/kg urine output following the first hour of surgery and there was no significant difference between groups (P = 0.8).

3.6. Postoperative Hemodynamic Variables. Postoperative hemodynamic variables are summarized in Table 4. Anesthesia charts and ICU records showed that patients in TIVA group continued to receive iv remifentanil infusion at a dose of 0.01 mcg/kg/min until their body temperature was 36.5°C (via active warming with heat blankets). During this period, which lasted for about 3 hours (160 ± 28 min), mean blood pressure and heart rate did not differ significantly between TIVA group (90 ± 15.3 mmHg, 81 ± 17 beats/min) and EA group (87 ± 14.2 mmHg, 76 ± 11 beats/min) (P = 0.4).

Charts showed that, after the warming period, mean blood pressure in TIVA group (103.5 ± 15.3 mmHg) significantly increased, when compared with EA group (85.9 ± 3.6 mmHg) (P = 0.0002). Also, mean heart rate in TIVA group (89.2 ± 17 beats/min) was significantly higher compared with EA group (76.4 ± 10.8 beats/min) (P = 0.018).

During the postoperative period, three patients in TIVA group (2 in the first day and 1 in the second day) had supraventricular tachycardia. These 3 patients were already receiving amiodarone treatment, and, according to charts, tachycardia was associated with pain, which was treated with rescue analgesics (tramadol 100 mg via iv infusion). There was no occurrence of hypotensive or bradycardic episode.

3.7. Postoperative Nutrition and Fluid Intake and Urine Output. The patients, who received less iv fluids due to short duration of surgery, received more fluids during the postoperative period in the ICU (P < 0.001). According to the ICU charts, all patients were ordered enteral feeding six hours after the end of the surgery. According to the charts, the standard meal consisted of low-fat, low-cholesterol, 2000 kcalories, and 60 grams of protein. The charts also showed that additional high energy oral nutritional supplements, four times a day (additional 1200 kcal/day), were ordered for non-diabetic patients, while diabetic patients were ordered additional diabetic supplements, four times a day (additional 960 kcal/day). Records showed that enteral feeding was not possible in 6 patients (33%) in TIVA group and one patient (7%) in EA group due to nausea, and vomiting was seen in 4 of these patients (all in TIVA group) despite treatment. Comparison of groups in terms of postoperative nausea and vomiting rate was statistically insignificant (P = 0.4).

According to the charts, these 7 patients were treated with ondansetron and received infusion of 5% dextrose solution until the next day. During the ICU stay, mean iv fluid treatment (2193 ± 247 mL/day) and urine output (0.56 ± 0.08 mL/kg/h) were similar in both groups (P = 1 and 0.7, resp.).

3.8. Postoperative Analgesia and Numeric Rating Scores. According to patient records, TIVA group received 50 mg of iv tramadol, every six hours. EA group received continuous epidural infusion of 0.25% bupivacaine. Numeric rating
scores were significantly high in TIVA group (5.4 ± 0.9, min: 4, max: 6) compared with EA group (1.8 ± 0.8, min: 0, max: 3) (P < 0.001). Also, 12 patients in TIVA group (70%) requested additional analgesics. Five of these patients received an iv infusion of 100 mg tramadol, and seven patients received intramuscular injection of 75 mg diclofenac sodium.

4. Discussion

This retrospective study showed that, compared to iv analgesia, epidural analgesia provides better pain control and enables earlier enteral feeding during postoperative period of endovascular repair of infrarenal abdominal aortic aneurysm.

4.1. Patient Demographics. Most patients were males. This is consistent with the current literature [6] since abdominal aortic aneurysm is more common in men of 65 years of age and older, and few women with an elective AAA are suitable for EVAR due to the anatomical differences [7].

Comorbidities were similar between groups, and hypertension, hyperlipidemia, and chronic obstructive pulmonary diseases were present in almost all patients. This is not surprising, since aneurysm is a vascular disease and smoking is strongly associated with formation and rupture of aortic aneurysm [1]. Although the chi-squared comparison of COPD presence between groups is not statistically significant, the abundance of COPD diagnosis in EA group is noticeable. Preanesthetic evaluation notes showed that all patients (except two) in the EA group had obstructive lung disease and were planned to be operated with regional anesthesia, because general anesthesia is more likely to cause atelectasis and postoperative respiratory failure [8]. One patient in the EA group had additional restrictive pathology (vital capacity: 600 mL, forced expiratory volume in the first second: 500 mL), needed continuous oxygen supply at a rate of 2 l/min to stay normoxic, and therefore had an ASA score of IV. To prevent atelectasis, this patient received intermittent (6 times a day, for 30 min) continuous positive airway pressure support through a mask during surgery and the first two postoperative days in the ICU.

4.2. Anesthesia Method. The choice of TIVA instead of an inhaled anesthetic was obligatory for this hospital, since the gas scavenging system deployed for the anesthetic machine was insufficient. Midazolam and propofol are widely used in combination with fentanyl in angiographic interventions and EVAR [9]. However, the duration of surgeries in this hospital varied (85–230 min). Therefore, propofol and remifentanil were selected, because both of these drugs are easy to titrate and allow rapid arousal and extubation [10].

4.3. Intraoperative Hemodynamic Variables. The presence of hypertension despite regular use of antihypertensive treatment and tachycardic episodes in about one of three patients shows that some of these surgeries were semielective. A more detailed look at the demographic data revealed that the five patients, who had a drop in mean blood pressure more than 25% during the surgery, had both hypertension and coronary artery disease and had hypertensive and tachycardic episodes during the preoperative period. According to preoperative anesthesia note, three of these patients were operated with TIVA, because the surgeons expected a difficult and long surgery. Intraoperative blood pressure and heart rate in these patients varied more than their counterparts, which were operated with epidural anesthesia. Also, exactly these three patients required more iv fluids (>2 liters, although the duration of surgery was below the mean) and are responsible for the (albeit statistically insignificant) difference in the iv fluid requirement between groups.

4.4. Postoperative Hemodynamic Variables and Nutritional Fluid Management. Mean blood pressure and heart rate were the same in both groups during immediate postoperative period, where the patients were warmed with heat blankets; the patients in EA group were treated with epidural infusion of local anesthetics, and the patients in TIVA group were still receiving analgesic dose of remifentanil. However, after the cessation of remifentanil infusion, mean blood pressure and heart rate in TIVA group increased. It is understood that this hemodynamic response, which included tachycardias, was related to pain, since these patients were treated with analgesics instead of antihypertensive or antiarrhythmic drugs.

On the contrary, according to the charts, the patients in EA group were hemodynamically stable throughout the ICU stay. This stability was not associated with fluids or blood products, as both fluid therapy and urine output were indifferent between groups, and none of the patients required postoperative transfusion. In our opinion, the hemodynamic

<table>
<thead>
<tr>
<th></th>
<th>TIVA (n = 17)</th>
<th>Epidural anesthesia (n = 14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of ICU stay (days)</td>
<td>5 ± 2</td>
<td>3 ± 1</td>
<td>NA</td>
</tr>
<tr>
<td>Total analgesic used</td>
<td>8.6 ± 1.7 mg remifentanil</td>
<td>54.5 ± 12.3 mg bupivacaine</td>
<td>NA</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>103.5 ± 15.3</td>
<td>85.9 ± 3.6</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mean heart rate (beats/min)</td>
<td>89.2 ± 17</td>
<td>76.4 ± 10.8</td>
<td>0.018</td>
</tr>
<tr>
<td>Median red blood cells transfused (units)</td>
<td>None</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Occurrence of nausea and vomiting</td>
<td>6 (33%)</td>
<td>1 (7%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table 4: Total postoperative analgesic drug, hemodynamic variables, and complications recorded during the postoperative intensive care unit (ICU) stay. Data are represented as median ± SD, mean ± SD, or number (percent).
stability was the result of improved analgesia. This was evident because none of the patients in EA group requested rescue analgesics, and the numeric rating scores were lower in EA group compared to TIVA group.

Only one patient in EA group experienced postoperative nausea and vomiting, whereas one-third of patients in TIVA group could not be fed enterally during the first day due to nausea and vomiting. The high occurrence of nausea may be attributed to tramadol, which is reported to cause dose-dependent nausea and vomiting, especially during the initial treatment [11]. This view may be supported by the fact that nausea was dominant after the warming period, where the patients in TIVA group continued to receive remifentanil infusion. Nausea may also have occurred due to inadequate analgesia, as there were recordings of nausea in 3 patients in TIVA group, who were treated with rescue infusion of tramadol due to tachycardia. Since these 3 patients were treated with additional tramadol dose, the mechanism of nausea in these patients may not be clear. Nausea may have occurred either due to inadequate analgesia or due to tramadol or due to the hemodynamic instability. In our opinion, epidural analgesia did not cause as much nausea as iv analgesia (although statistically not significant), and hemodynamic stability and earlier feeding may be the main reasons of the significantly shorter stay in the ICU.

5. Conclusions

In conclusion, this retrospective case-control study found that epidural anesthesia and postoperative epidural analgesia better reduce postoperative pain compared with total iv anesthesia and systemic analgesia, with similar effects on hemodynamic status.

Conflict of Interests

The authors do not have any conflict of interests regarding the content of the paper.

References

Clinical Study

Comparison of the Effect of Lidocaine Adding Dexketoprofen and Paracetamol in Intravenous Regional Anesthesia

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Objective. Comparison of dexketoprofen and paracetamol added to the lidocaine in Regional Intravenous Anesthesia in terms of hemodynamic effects, motor and sensorial block onset times, intraoperative VAS values, and analgesia requirements.

Method. The files of 73 patients between 18 and 65 years old in the ASA I-II risk group who underwent hand and forearm surgery were analyzed and 60 patients were included in the study. Patients were divided into 3 groups: Group D (𝑛= 20), 3 mg/kg 2% lidocaine and 50 mg/2 mL dexketoprofen trometamol; Group P (𝑛= 20), 3 mg/kg 2% lidocaine and 3 mg/kg paracetamol; Group K (𝑛= 20), 3 mg/kg 2% lidocaine. Demographic data, motor and sensorial block times, heart rate, mean blood pressure, VAS values, and intraoperative and postoperative analgesia requirements were recorded.

Results. Sensorial and motor block onset durations of Group K were significantly longer than other groups. Motor block termination duration was found to be significantly longer in Group D than in Group K. VAS values of Group K were found higher than other groups. There was no significant difference in VAS values between Group D and Group P. Analgesia requirement was found to be significantly more in Group K than in Group P. There was no significant difference between the groups in terms of heart rates and mean arterial pressures.

Conclusion. We concluded that the addition of 3 mg/kg paracetamol and 50 mg dexketoprofen to lidocaine as adjuvant in Regional Intravenous Anesthesia applied for hand and/or forearm surgery created a significant difference clinically.

1. Introduction

Regional Intravenous Anesthesia (RIVA) was first applied by German surgeon, August K.G. Bier, in 1908, and this technique was defined as Bier block [1]. RIVA is generally preferred for patients who will have upper extremity surgery due to advantages such as providing a blood free surgery site, rapid onset and termination of the anesthetic effect, lack of necessity of severe sedation, and general anesthesia and easy application [2, 3]. Ketorolac, tenoxicam, paracetamol, clonidine, myorelaxant drugs, and opioids were added into local anesthetic agents as adjuvant to increase block quality in RIVA, to reduce tourniquet pain, to provide postoperative analgesia, and to reduce the dose of local anesthetic agent administrated [4–7].

Although molecular mechanism is not known well, intravenous paracetamol (perfalgan) is used for mild and intermediate postoperative pain. It is a nonopioid analgesic which reduces the opioid quantity used for severe pain [8–10].

Dexketoprofen trometamol is a nonselective NSAII with analgesic, antipyretic, and anti-inflammatory characteristics of which the parenteral form was developed in 2003 [11].

In the present study, we aimed to compare sensorial block onset and return periods, motor block onset and return periods, the block quality that appeared, preoperative and postoperative vital signs, and the need for intraoperative and postoperative analgesia for lidocaine-paracetamol combination and lidocaine-dexketoprofen combination retrospectively in the light of findings that we have obtained by the examination of patient files who have undergone hand and/or forearm surgery through the RIVA method in our university.

2. Material and Method

Records of adult patients referred to Karadeniz Technical University, Faculty of Medicine, Orthopedics Clinic and who have undergone hand and forearm surgery were enrolled.
Once the study protocol was approved by the ethics committee of the Karadeniz Technical University in accordance with the 2nd Helsinki Declaration (date: 26.11.2012, meeting no.: 2012/125, resolution no.: 02), the anesthesia records of the patients were selected and the patients were enrolled in the study. Adult patients who have been examined routinely by anamnesis and physical examination and classified as ASA I and II according to preoperative physical status classification recommended by the American Society of Anesthesiologists were included in the study. Anesthesia records and hospital archive records of 73 patients between the age of 18 and 60 to whom regional intravenous anesthesia (RIVA) was applied were examined. The data of 13 patients were not included in the study because they did not comply with the study criteria, and the data of 60 patients were examined.

Exclusion criteria were (i) analgesic drug treatment in the previous 24 h, (ii) history of allergy to study medications, (iii) any neurological deficit in the upper extremities, and (iv) the presence of any contraindications to IVRA.

Age, gender, ASA, operation duration, and tourniquet periods were recorded from hospital archive files and anesthesia records.

It was observed from the files that premedication by 0.15 mg/kg midazolam (im) was performed before the surgery and RIVA (Regional Intravenous Anesthesia) was applied by monitoring average arterial pressure, heart rate, and peripheral oxygen saturation parameters.

The patients were divided into the following groups according to the medications used for RIVA procedure.

**Groups**

1. (Group D) lidocaine-dexketoprofen group: patients \(n=20\) on whom RIVA was performed by the addition of 3 mg/kg 2% lidocaine and 50 mg/2 mL dexketoprofen trometamol (Arveles 50 mg/2 mL; UFSA Pharmaceuticals, Topkapı/Istanbul, Turkey) diluted with 0.9% normal saline to a total volume of 40 mL.

2. (Group P) lidocaine-paracetamol group: patients \(n=20\) on whom RIVA was performed by the addition of 3 mg/kg 2% lidocaine and 3 mg/kg paracetamol (Percalgan 1000 mg/100 mL vial, Bristol-Myers Squibb, France) diluted with 0.9% normal saline to a total volume of 40 mL.

3. (Group K) lidocaine-control group: patients \(n=20\) on whom RIVA was performed by 3 mg/kg 2% lidocaine diluted with 0.9% normal saline to a total volume of 40 mL.

Records of these patients in three groups were examined.

It was observed that the tourniquet pressure of the RIVA solution was kept as 100 to 150 mmHg higher than systolic arterial pressure or at 250 to 300 mmHg, study medications were administrated within 90 seconds, sensorial block was assessed by a pinprick test every 30 seconds, sensorial examination of antebrachial, radial, ulnar, and median nerve dermatomes was conducted, and the motor block was assessed via the Modified Bromage Scale (MBS) by inability to move the wrist and fingers voluntarily by asking the patients if they could move their wrist and fingers. It was also observed that sensorial and motor block onset times and termination times of the blocks were recorded and their mean arterial pressures (MAP), heart rates, pulse oximeter, and oxygen saturations (SpO2) were recorded and their records were evaluated.

It was detected that VAS (Visual Analog Scale) and Ramsey sedation scale were used before and at the 5th, 10th, 20th, and 30th minutes after tourniquet procedure and at the 5th, 10th, 15th, and 30th minutes and the 1st and 2nd hours after the tourniquet was opened for pain and sedation level measurements. Furthermore, intraoperative and postoperative analgesic requirements of the patients who had analgesic administration as fentanyl 1 μg/kg when intraoperative VAS was over 3 were examined. It was observed that 500 mg oral Parol tablet was given to the patients whose pain sustained postoperatively and 50 mg contramal tablet for those whose pain was persistent. It was detected that interviews were performed with the patients after their discharge and questions related to operation comfort, quality, and incision pain were asked. Side effects that the patients had, such as nausea, vomiting, dyspeptic complaints, skin rash, and tinnitus, were examined from hospital archive files and anesthesia records.

Statistical data analysis was carried out by using “Statistical Package for Social Sciences” (SPSS) for Windows Release 13.0 program. K-Square was used for comparison of qualitative data; compliance to normal distribution in comparison of the data obtained by measurement was performed through the Kolmogorov-Smirnov test; student’s t-test was used if it complied with the normal distribution and the Mann-Whitney U-test was used if it did not comply. Variance analysis of repetitive measurements or the Friedman test was used for comparison of measurements which continue from the beginning. Data obtained through measurements were expressed with mean standard deviation and data obtained by count was expressed as %. Significance level was accepted as \(P < 0.05\).

### 3. Results

No difference was detected between the groups in terms of age, gender, ASA, operation durations, and tourniquet periods (Table 1).

No significant difference was found between the groups in terms of intraoperative and postoperative time values, heart rates, and mean arterial pressure values.

There was no statistically significant between-group type of surgery (Table 2).

Sensory block onset durations of Group K were significantly longer than other groups \((P < 0.05)\). There was no significant difference between Groups D and P in terms of sensorial block onset periods. No significant difference existed between the groups in terms of sensorial block termination times as well (Table 3).

Motor block onset durations of Group K were significantly longer than other groups \((P < 0.05)\). There was no significant difference between Groups D and P in terms
Table 1: Demographic data, total operation time and total tourniquet, and application time (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Group K control (n = 20)</th>
<th>Group D dexketoprofen (n = 20)</th>
<th>Group P paracetamol (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>32.81 ± 12.15</td>
<td>35.65 ± 13.77</td>
<td>36.15 ± 13.55</td>
</tr>
<tr>
<td>Sex-male</td>
<td>13 (%65)</td>
<td>15 (%75)</td>
<td>15 (%75)</td>
</tr>
<tr>
<td>Sex-female</td>
<td>7 (%35)</td>
<td>5 (%25)</td>
<td>5 (%25)</td>
</tr>
<tr>
<td>ASA-1*</td>
<td>15 (%75)</td>
<td>16 (%80)</td>
<td>15 (%75)</td>
</tr>
<tr>
<td>ASA-2*</td>
<td>5 (%25)</td>
<td>4 (%20)</td>
<td>5 (%25)</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>39.0 ± 8.09</td>
<td>40.20 ± 9.29</td>
<td>48.55 ± 11.68</td>
</tr>
<tr>
<td>Tourniquet time (min)</td>
<td>54.3 ± 9.0</td>
<td>56.25 ± 10.25</td>
<td>66.15 ± 11.65</td>
</tr>
</tbody>
</table>

* ASA: American Society of Anesthesiologists physical classification status.

Table 2: Types of operations performed.

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Group K Control (n = 20)</th>
<th>Group D dexketoprofen (n = 20)</th>
<th>Group P paracetamol (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger finger</td>
<td>8</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>5</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Tendon release</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Cyst excision</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3: Block onset times and block regression times of the groups (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Group K control (n = 20)</th>
<th>Group D dexketoprofen (n = 20)</th>
<th>Group P paracetamol (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory block onset time (min)</td>
<td>4.70 ± 1.38*</td>
<td>3.46 ± 1.14</td>
<td>4.6 ± 1.78</td>
</tr>
<tr>
<td>Sensory block regression time (min)</td>
<td>4.20 ± 1.73</td>
<td>4.1 ± 1.37</td>
<td>3.9 ± 1.99</td>
</tr>
<tr>
<td>Motor block onset time (min)</td>
<td>9.40 ± 4.23*</td>
<td>8.65 ± 2.97</td>
<td>10.05 ± 2.72</td>
</tr>
<tr>
<td>Motor block regression time (min)</td>
<td>4.70 ± 2.29</td>
<td>8.85 ± 1.72*</td>
<td>6.40 ± 3.18</td>
</tr>
</tbody>
</table>

*P < 0.05 according to Group D and Group P.

of sensorial block onset periods. Motor block termination duration was found significantly longer in Group K than Group D (P < 0.05) (Table 3).

VAS values of Group K were higher than other groups (P < 0.05). There was no significant difference in VAS values between Group D and Group P (Figure 1).

Intraoperative analgesia requirements were significantly more in Group K than Group P and Group D. Intraoperative analgesia was required for 8 patients in Group K and for 4 patients in Group D. Postoperative analgesia requirements were significantly more in Group K than Group P and Group D. Postoperative analgesia was required for 9 patients in Group K and for 5 patients in Group D (Figure 2).

It was also found that 1 patient had skin rash and 2 patients had bradycardia during their follow-ups. There was no significant difference between the groups (P > 0.05).

4. Discussion

Regional intravenous anesthesia is a common regional anesthesia method used for upper extremity surgery. It was detected that the addition of 3 mg/kg paracetamol and 50 mg dexketoprofen into local anesthetic agents as adjuvant in regional intravenous anesthesia performed for hand and/or forearm surgery reduced VAS values and shortened sensorial block onset time and motor block return time significantly...
was detected following tourniquet opening [15]. Where sufentanil was added to lidocaine; however, dizziness motor block onset time was found to be shorter in the group agents for RIVA are prilocaine and lidocaine [12–14].

Low concentration and dose. To local anesthetic agent to support as sufficient anesthesia on system toxicity. Different adjuvant medications were added to local anesthetic agents to support a sufficient anesthesia on low concentration and dose.

In the literature scan, the most preferred local anesthetic agents for RIVA are prilocaine and lidocaine [12–14]. In the study conducted by Fahim et al., sensorial and motor block onset time was found to be shorter in the group where sufentanil was added to lidocaine; however, dizziness was detected following tourniquet opening [15].

Acalovschi et al. [16] and Fahim et al. added 100 mg tramadol into lidocaine [15], whereas Tan et al. [17] and Özcan et al. [18] added 50 mg tramadol appropriate and detected that the sensorial block onset time shortened.

There are studies indicating that the addition of dexamethasone might prolong sensorial and motor block in RIVA. Bigat and Boztuğ detected in their RIVA study conducted with dexamethasone, a steroid, by considering inflammatory steps during pain physiopathogenesis that 8 mg dexamethasone added to 3 mg/kg lidocaine increased anesthesia quality and provided a significant anesthesia on the first postoperative day [19].

Sen et al. concluded in their RIVA study by adding lornoxicam into 3 mg/kg lidocaine that sensorial and motor block onset time was shorter, sensorial and motor block return time was longer, and the necessity for first anesthesia for tourniquet pain was longer and total analgesic consumption was reduced in the group (L-IVRA) where lornoxicam was added to lidocaine when compared with other groups (control and L-IV) [20].

When the literature was examined, studies where paracetamol and dexketoprofen were added to local anesthetic agents in RIVA are rare [7, 21–23]. There is no study where two adjuvants were compared in the literature.

There is only one study where dexketoprofen was used as adjuvant in RIVA in the literature. Yurtlu et al. [23] detected in their study with dexketoprofen in lidocaine in RIVA that sensorial and motor block onset times were shorter, return times were longer, intraoperative analgesia requirement was less, intraoperative and postoperative VAS values were lower, and no difference existed between hemodynamic values. Similarly, motor block and sensorial block onset periods were found to be shorter in our study in patients to whom dexketoprofen was added when compared with the group without adjuvant addition. Furthermore, the need for intraoperative analgesia and VAS values were similarly found to be lower [23].

There are three studies in the literature where paracetamol was used as adjuvant in RIVA.

Ko et al. [7] reported in their RIVA study by adding 300 mg of intravenous paracetamol into 0.5% lidocaine that although sensorial block onset time was shorter in the group where paracetamol was added when compared with the control group, there was no difference in terms of sensorial block return times after the operation, intraoperative analgesia requirement was less, and intraoperative and postoperative VAS values were lower. Similarly, motor block and sensorial block onset periods were found to be shorter in our study in patients to whom paracetamol was added when compared with the group without adjuvant addition. Furthermore, the need for intraoperative analgesia and VAS values were similarly found to be lower.

In another study conducted by Celik et al. [22] through the addition of 200 mg of intravenous paracetamol to lidocaine (3 mg/kg), it was reported that there was no difference between sensorial and motor block onset and return times; furthermore, requirement of intraoperative analgesia was less. Similarly, we also found that the intraoperative analgesia requirement was less.

Sen et al. [21] did not find any difference between sensorial block onset time, motor block onset, and return time between the group where paracetamol was added and the control group in their RIVA study where they added 300 mg of intravenous paracetamol into lidocaine (3 mg/kg), and they reported that postoperative sensorial block return time was longer in the paracetamol group and intraoperative analgesia requirement was less.

When we assess the studies for possible adverse events and complications developed, no adverse events were detected in the study conducted by Ko et al. [7]. Sen et al. [21] reported nausea in three patients in their study. In case of follow-ups of our study, rash on one patient and bradycardia on two patients were detected. We could not find any significant difference between the side effects developed and groups.

There is no study in the literature in which motor and sensorial block periods, intraoperative analgesia requirement, hemodynamic monitoring, and side effects developed were compared to adding paracetamol and dexketoprofen to lidocaine in regional intravenous anesthesia. We analyzed anesthesia records and hospital records of the patients for
whom 50 mg of dexketoprofen and 3 mg/kg paracetamol were added to 3 mg/kg in regional intravenous anesthesia.

According to our results, the addition of 50 mg dexketoprofen and 3 mg/kg paracetamol to 3 mg/kg lidocaine shortened the onset of motor block and provided prolonged motor block and sensorial block termination periods when compared with the patients to whom adjuvant was not added in line with the studies conducted. Furthermore, it was found that it reduced intraoperative analgesia need and intraoperative and postoperative VAS values were lower; no significant difference existed in hemodynamic parameters. In the study conducted, no significant value was found when groups that adjuvant was added to were compared.

Consequently, it was found that the addition of paracetamol and dexketoprofen to the lidocaine in regional intravenous anesthesia applied for hand and/or forearm surgery does not create any significant difference; however, it is more successful clinically according to the group without adjuvant addition.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


Clinical Study

The Effects on Sensorial Block, Motor Block, and Haemodynamics of Levobupivacaine at Different Temperatures Applied in the Subarachnoid Space

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Aim. To evaluate the effects of 0.5% levobupivacaine at 37°C preheated from room temperature, on sensorial block, motor block, and haemodynamics in patients undergoing transurethral prostate resection (TUR-P).

Material and Method. The patients were randomly allocated to two groups: Group I patients were injected with 3 mL 0.5% levobupivacaine solution which had been kept at room temperature for at least 24 hours and Group II patients were injected with 3 mL 0.5% levobupivacaine solution which had been kept at 37°C for at least 24 hours. The patients were examined in terms of sensorial block, motor block, haemodynamic profile, and incidence of side effects.

Results. No significant difference was found between the groups in terms of demographic data. The time to reach T10 sensory block and the time of starting motor block were found to be significantly shorter in Group II. The duration of sensory block over T10 and T6, the duration of L1 regression, the duration of the sensory block, and the regression time of the motor blocks from 3 to 2 were found to be longer in Group II. Conclusion. The use of 0.5% levobupivacaine spinal anaesthesia heated to 37°C accelerated the start of sensory and motor block.

1. Introduction

Although there are in vitro studies showing changes in the density of local anaesthetic (LA) at different temperatures [1–6], there are a limited number of studies showing the effects of these changes in density from different temperatures on spinal anaesthesia clinical results [7–9].

The decrease in density in inverse proportion to the increase of the liquid temperature was explained by Davis and King [10] giving examples of the relationship between temperature and density (Table I).

A curvilinear reduction was seen in the density with increased temperature of the LA solution. Changes occurring in density with reflected in the baricity [1–5, 11]. Injections of room temperature LA solutions into body temperature cerebrospinal liquid (CSF) cause an immediate local reduction in CSF temperature (2–3°C with 2.4 mL bolus; 6–8°C with 12 mL bolus) but the CSF returns to normal temperature within 2 min. This happens before spinal root fixation of the local anaesthetics [1–3]. Therefore when there is synchronisation of the temperature, the local anaesthetic solution in the CSF will display a mild hyperbaric property and thus the position of the patient will affect the distribution of the local anaesthetic.

Results from the effect of temperature are related more to the use of solutions without additives. For example, in a study by McLeod using a mechanical oscillation resonance method to investigate the relationship between temperature and density, it was determined that 37°C densities
While \( pK_a \) the block, and lengthens the duration of the block [12, 13]. This speeds up the start of the effect, increases the quality of an increase in the fraction of nonionised local anaesthetic.

With 7% dextrose, the 25°C and 37°C densities of 0.5% bupivacaine were equal (1,028 g/cm³) [9]. The temperature of local anaesthetics has an effect on \( pK_a \) values. Increased temperature of local anaesthetics by decreasing \( pK_a \) approaches the physiological pH and causes an increase in the fraction of nonionised local anaesthetic. This speeds up the start of the effect, increases the quality of the block, and lengthens the duration of the block [12, 13]. While \( pK_a \) is 7.92 in lidocaine at 25°C, at 40°C it is 7.57 [14]. At 10°C, the \( pK_a \) value of bupivacaine is 8.49 and at 38°C, it is 7.92. The \( pK_a \) value of mepivacaine at 10°C is 8.02 and at 38°C it falls to 7.55 [15].

On a thermodynamic basis, when increased temperature increases molecular kinetic energy, the number of moving particles increased [16]. Thus increased temperature causes increased molecular activity of the local anaesthetic solution and facilitates distribution in the CSF and higher levels of spinal anaesthesia are reached [9].

On the other hand, levobupivacaine has less affinity and strength of depressant effects on to myocardial and central nervous vital centers and a superior pharmacokinetic profile. Clinically, levobupivacaine is well tolerated in a variety of regional anaesthesia.

In the current study, using a 0.5% levobupivacaine solution kept at either room temperature (20–24°C) or body temperature (36–37°C) for 24 hours and then injected into the subarachnoid space in patients undergoing TUR-P for BPH, it was aimed to compare the effects of this temperature difference on spinal anaesthesia characteristics from motor and sensory block starting time, maximum block level, duration of the block, and haemodynamic parameters.

### Table 1: The effect of heat on liquid density.

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>Density (gr/mL)</th>
<th>Difference (gr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.9991</td>
<td>0.0009</td>
</tr>
<tr>
<td>25</td>
<td>0.9971</td>
<td>0.0020</td>
</tr>
<tr>
<td>37</td>
<td>0.9934</td>
<td>0.0037</td>
</tr>
</tbody>
</table>

(0.99944 for 0.5% bupivacaine, 1,00024 for 0.5% levobupivacaine, and 0.99953 mg/mL for 0.5% ropivacaine) were lower than 23°C densities (1,00376 for 0.5% bupivacaine, 1,00419 for 0.5% levobupivacaine, and 1,00380 mg/mL for 0.5% ropivacaine) [4].

The levels of sensory block starting time, maximum block level, and sensory block level were defined as the dermatome and above) had been reached, the patient was put into the lithotomy position and the surgery was allowed to start. In cases where the sensory block did not reach \( T_{10} \), it was decided to administer general anaesthesia.

From the moment, the patient entered the operating theatre and throughout the operation a record was made of systolic, diastolic, and mean blood pressure, heart rate, and \( \text{SpO}_2 \) (at 5 min intervals for the first 30 min, at 10 min intervals for the next 30 mins, then at 15 min intervals up to 90 mins, and at 30 min intervals thereafter).

Patients were monitored for any side effects of nausea, vomiting, bradycardia, hypotension, and reduced \( \text{SpO}_2 \) (<93%). Throughout the monitoring, if systolic blood pressure was determined to have dropped by more than 30% of the preoperative basal values, a rapid iv infusion of 0.9% saline was administered and if necessary a 10 mg iv bolus of ephedrine at 1 min intervals and if heart rate fell below 50/min, a 0.5 mg iv bolus of atropine was administered. If nausea and vomiting were determined, metoclopramide was given as 10 mg iv and a fall of \( \text{SpO}_2 \) below 93% was evaluated as hypoxia and 4 l/min⁻¹ oxygen was administered via a face mask.

The levels of sensory block and motor block were recorded by evaluations at 5 min intervals for the first 30 min, at 10 min intervals for the next 30 mins, then at 15 min intervals up to 90 min, and at 30 min intervals thereafter.

The sensory block level was defined as the dermatome where the sensory response was lost with the pinprick test on the bilateral anterior axillary line.

The time taken for the sensory block to reach \( T_{10} \); the time taken for the sensory block to reach the \( T_{10} \) dermatome from the injection of the LA solution into the subarachnoid space; maximum sensory block level; the highest level dermatome where the sensory response was lost with the pinprick test;
the time to reach maximum sensory block; the time taken to reach the highest sensory block level from the injection of the LA solution into the subarachnoid space; the duration of the sensory block at T_{10} and above; the total time that there was no sensory response with the pinprick test at T_{10} and above; the duration of the sensory block at T_{6} and above; 2 segment regression time; the mean time taken for the sensory block to reduce to two dermatomes below the highest level; L_{1} regression time; the mean time taken for the distribution sensory block to fall from the highest level to the L_{1} dermatome level. The mean times of the rising sensory block with the LA injection and the fall to L_{1} dermatome were evaluated and recorded.

The motor block was evaluated with the Modified Bromage Score (0 = no paralysis the patient can fully flex the foot and knee, 1 = the patient cannot raise a straight leg, the knee and foot can be moved, 2 = the knee cannot be brought to flexion, only the foot can be moved, 3 = foot joints or toes cannot be moved, total paralysis).

The 10-minute Bromage score was evaluated and recorded as the degree of motor block 10 minutes after the LA injection into the subarachnoid space. The time of starting motor block; the time taken from the LA injection into the subarachnoid space for full motor block (Bromage score 3) to form in the lower extremities. Bromage score 3 to 2 regression time; the time taken from full motor block of the lower extremities to a return of the ability to move the feet.

At the end of surgery, the surgeon evaluated the ease of the operation as poor (0), moderate (1), or good (2).

An evaluation was requested from the patient postoperatively in the form of (1) I would not prefer this type of anaesthesia in the future or (2) I would prefer this type of anaesthesia in the future.

2.1. Statistical Analysis. Data analysis was made with statistical package for social science (SPSS) 11.5 package programme. It was decided to take at least 12 subjects for each group. The distribution of the data obtained from the measurements was examined with the Shapiro Wilk test for conformity to normal distribution. The features of the descriptive statistics obtained from the measurements are given as mean ± standard deviation or mean (minimum-maximum) and the categorical variables are shown as number of cases and percentages (%).

Whether there was any statistically significant difference between the groups in normally distributed continuous variables was examined with Student’s t-test and with the Mann Whitney U test for nonnormal distribution continuous variables. Repeated measures variance analysis was used to evaluate any statistically significant difference in repeated measurements in the groups. Where the statistical result of the repeated measures variance analysis was found to be significant, the Bonferroni correction multiple comparisons test was used to determine the reason for the difference at the time of measurement. For categoric comparisons, Chi-Square or Fisher’s Exact probability test was used. A value of P < 0.05 was accepted as statistically significant for all the results.

3. Results

The demographic characteristics (age, weight, and height) of the patients, ASA classifications and duration of surgery are given in Table 2. There was no statistically significant difference between the groups.

Sensory block of T_{10} or above was reached as the criteria for surgery to commence for all patients. The duration of the sensory block at T_{10} or above was 97.33 ± 26.31 min for Group I which was shorter than the 140.57 ± 22.30 min in Group II. The difference between the groups was found to be statistically significant (P < 0.001).

The difference between the groups in respect of the duration of the sensory block was found to be statistically significant (P = 0.004) (Table 3). The distributions of maximum sensory block levels according to the groups are shown in Table 4.

While the median level of the maximum sensory block level in Group I was T_{8} (mean ± SD; 7.86 ± 1.07), it was T_{6} in Group II (mean ± SD; 4.16 ± 0.91) (Figure 1). The difference between the groups was found to be statistically significant (P < 0.001).

The sensory block levels of the groups according to the time of evaluation are shown in Figure 2. At each evaluation time, the sensory block levels of Group I were found to be lower than those of Group II. At all the evaluation times, the
Table 2: Demographic data, ASA classification, and duration of operation for all the patients.

<table>
<thead>
<tr>
<th></th>
<th>Group I (room temperature) n = 30</th>
<th>Group II (37°C) n = 30</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages (years)</td>
<td>65.90 ± 10.72</td>
<td>65.57 ± 7.44</td>
<td>0.889</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>70.83 ± 9.90</td>
<td>71.50 ± 11.60</td>
<td>0.812</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.37 ± 4.97</td>
<td>169.10 ± 5.44</td>
<td>0.844</td>
</tr>
<tr>
<td>ASA I/II/III</td>
<td>2/23/5</td>
<td>1/26/3</td>
<td>0.598</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>43.23 ± 10.31</td>
<td>45.90 ± 13.14</td>
<td>0.386</td>
</tr>
</tbody>
</table>

Values are given as mean ± standard deviation (mean ± SD).

Table 3: Comparison of the sensory block data.

<table>
<thead>
<tr>
<th></th>
<th>Group I (room temp.) n = 30</th>
<th>Group II (37°C) n = 30</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to reach T₁₀ (min)</td>
<td>13.86 ± 3.73</td>
<td>6.40 ± 1.61</td>
<td>0.000*</td>
</tr>
<tr>
<td>Time to reach maximum sensory block (min)</td>
<td>24.37 ± 5.90</td>
<td>22.27 ± 4.27</td>
<td>0.178</td>
</tr>
<tr>
<td>Duration of sensory block at or above T₁₀ (min)</td>
<td>97.33 ± 26.31</td>
<td>140.57 ± 22.30</td>
<td>0.000*</td>
</tr>
<tr>
<td>Duration of sensory block at or above T₆ (min)</td>
<td>5.00 ± 14.14</td>
<td>80.00 ± 23.92</td>
<td>0.000*</td>
</tr>
<tr>
<td>Duration of 2 segment regression (min)</td>
<td>77.80 ± 23.40</td>
<td>69.40 ± 17.13</td>
<td>0.084</td>
</tr>
<tr>
<td>Duration of L₁ regression (min)</td>
<td>148.13 ± 24.77</td>
<td>167.73 ± 23.48</td>
<td>0.003*</td>
</tr>
<tr>
<td>Duration of sensory block (min)</td>
<td>172.50 ± 24.16</td>
<td>190.00 ± 24.63</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

Values are given as mean ± standard deviation (mean ± SD).
* Statistical significance of difference between mean values (P < 0.05).

A statistically significant difference was determined between the repeated HR measurements in Group I (P < 0.001). The statistically significant decrease in mean HR in this group started from 25 min (P < 0.01). In Group II, a statistically significant difference was determined between the repeated HR measurements (P = 0.003). In this group, the statistically significant decrease in mean HR in this group started from 20 min (P < 0.05).

When the mean systolic blood pressure (SBP) measurements obtained throughout the monitoring were compared, a statistically significant difference was determined between the groups (P = 0.017). In general, the SBP level of Group I was higher than that of Group II.

When the mean SBP values of the groups were compared according to the time of evaluation, no statistically significant difference was determined in the preblock values (P = 0.436). A statistically significant reduction was determined between the repeated SBP measurements in Group I (P = 0.003). Within this group, a statistically significant reduction occurred in the mean SBP from 40 min on P < 0.01. A statistically significant reduction was determined between the repeated SBP measurements in Group II (P < 0.001). Within this group, a statistically significant reduction occurred in the mean SBP from 10 min on P < 0.01.

When the mean diastolic blood pressure (DBP) measurements obtained throughout the monitoring were compared, a statistically significant difference was determined between the groups (P = 0.048). A statistically significant reduction was determined between the repeated DBP measurements in Group I (P < 0.05).

When the mean HR measurements obtained throughout the monitoring were compared, there was no statistically significant difference between the groups (P = 0.818 > 0.05).

A statistically significant difference was determined between the repeated DBP measurements in Group I (P < 0.001).
Within this group a statistically significant reduction occurred in the mean DBP from 30 min on \( P < 0.01 \). A statistically significant reduction was determined between the repeated DBP measurements in Group II \( P < 0.001 \). Within this group, a statistically significant reduction occurred in the mean DBP from 5 min on \( P < 0.05 \).

When the mean blood pressure (MBP) measurements obtained throughout the monitoring were compared, a statistically significant difference was determined between the groups \( P = 0.047 \). In general, the MBP level of Group I was higher than that of Group II.

When the mean MBP values of the groups were compared according to the time of evaluation, no statistically significant difference was determined in the preblock values \( P = 0.771 \).

A statistically significant reduction was determined between the repeated MBP measurements in Group I \( P = 0.006 \). Within this group, a statistically significant reduction occurred in the mean MBP from 75 min on \( P = 0.043 \). A statistically significant reduction was determined between the repeated MBP measurements in Group II \( P < 0.001 \). Within this group a statistically significant reduction occurred in the mean MBP from 5 min on \( P < 0.05 \).

No statistically significant difference was determined between the groups in the saturation (SpO\(_2\)) measurements obtained throughout the monitoring period \( P = 0.235 > 0.05 \).

There was similar prevalence of hypotension, bradycardia, nausea, and vomiting between the groups \( P \text{ values: } 0.112, 0.554, 1.000, \) and 1.000, resp.). Comparison was not made for these side effects in any case where there was no reduction in saturation level \( \text{SpO}_2 < 93\% \).

While there was no need for ephedrine in Group I, when 4 patients in Group II required the administration of ephedrine, a reduction in SBP values was determined. The difference between the group was not found to be statistically significant \( P = 0.112 \).

In 2 patients in Group I and 1 patient in Group II, when there was a need for the administration of atropine, HR was determined to have dropped below 50/min. The difference between the group was not found to be statistically significant \( P = 1.000 \).

There was no difference between the groups in terms of patient and surgeon satisfaction levels \( P = 1.000 \).

### 4. Discussion

Various factors have been reported to affect the intrathecal distribution of local anaesthetic solutions [17, 18]. Features such as the concentration of the injected solution, volume, baricity, density, and temperature are important amongst these factors [11, 17].

In a search of literature, no in vivo studies were found which researched the effects on clinical results of 0.5% levobupivacaine at different temperatures on spinal anaesthesia distribution. However, in vivo and in vitro studies conducted on nerve blocks have shown levobupivacaine to be as powerful as bupivacaine and provides similar sensory and motor block [19–21].

According to Richardson and Wissler [22], the upper level of hypobaricity in males is 1.00028 g/mL and hyperbaricity lower level is 1.00100 g/mL [23]. When the measurements of this researcher are used, 0.5% levobupivacaine solution is mildly hyperbaric at 23°C (density: 1.00419 (0.00002) mg/mL) and mildly hypobaric at 37°C (density: 1.00024 (0.00009) mg/mL).

In the current study, from the intrathecal application in a sitting position of 3 mL of 0.5% levobupivacaine solution at different temperatures (37°C and room temperature), the mean maximum sensory block levels of the 37°C and room temperature groups were found to be \( T_4, 16 \pm 0.91 (T_3-T_5) \) and \( T_7, 86 \pm 1.07 (T_5-T_9) \), respectively. This difference in the mean maximum sensory block levels was statistically significant. All the sensory block levels of the evaluation times in Group II were statistically significantly high compared to Group I.

When compared with CSF density, that 0.5% levobupivacaine solution is mildly hyperbaric at 37°C and mildly hypobaric at room temperature [22] may explain the higher maximum sensory block levels obtained in Group II. On a thermodynamic basis, the increased temperature of levobupivacaine increases molecular kinetic energy and thereby the number of active particles which is also considered to have a possible contribution to the higher sensory block levels.

In the current study, the standard deviation (SD) values of the mean maximum sensory block levels in Group I and Group II were ±0.91 and ±1.07 and minimum–maximum values were \( T_6-T_3 \) and \( T_9-T_5 \), respectively. It is thought that the

### Table 4: Distribution of maximum sensory block levels according to the groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Maximum level of sensory block</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( T_1 )</td>
<td>( T_4 )</td>
</tr>
<tr>
<td>I (room temp.)</td>
<td>Number</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>0</td>
</tr>
<tr>
<td>II (37°C)</td>
<td>Number</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>23.3</td>
</tr>
<tr>
<td>Total</td>
<td>Number</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>11.7</td>
</tr>
</tbody>
</table>
SD values of Group II being lower than those of Group I and the minimum-maximum values being close to each other is because the maximum sensory block level may be more easily predicted.

When the mean highest sensory block levels are considered (Group II, $T_{10}$; 16; Group I, $T_{10}$, 86), it is seen that the time per segment to reach these levels was shorter in the 37°C group. In addition, the time taken to reach the sensory block level of $T_{10}$ in Group II determined in this study was statistically significantly shorter compared to Group I (13.86 ± 3.73). These results show that heating levobupivacaine to 37°C increased the speed of the sensory block. This result can be explained by the temperature increase lowering the density and thereby the baricity. Also, by lowering the $pK_a$ value of increased temperature local anaesthetics, the physiological pH is approached [12–15] and it is thought that the start of the effect is accelerated by increased non-ionised fraction resulting from the reduced $pK_a$ created in 37°C levobupivacaine.

In the current study, the 2 segment regression time for 0.5% levobupivacaine was determined as shorter in Group II (69.40 ± 17.13 min) compared to Group I (77.80 ± 23.40 mins). No statistically significant difference was determined in this difference of 2 segment regression. It is thought that the shorter time of 2 segment regression in Group II can be explained by greater distribution within the CSF of the local anaesthetic solution at this temperature and because of this lower concentration, the regression was accelerated.

Another means of evaluating sensory block regression is to determine the time of the sensory block at a specified dermatome level. In the current study, the mean time of the 0.5% levobupivacaine sensory block above $T_8$ and $T_{10}$ was found to be 80.00 ± 23.92 min and 140.57 ± 22.30 min, respectively, in Group II and 5.00 ± 14.14 min and 97.33 ± 26.31 min, respectively, in Group I. The difference in these times was found to be statistically significantly longer in Group II.

It is thought that the shorter times of the sensory block at these levels may be due to 0.5% levobupivacaine at room temperature being mildly hyperbaric and the low number of patients in whom the sensory block was able to exceed $T_{10}$ and $T_8$ segments from the intrathecal application in a sitting position.

In the current study, the duration of $L_1$ regression was determined as 167.73 ± 23.48 min in Group II and 148.13 ± 24.77 min in Group I with Group II being statistically significantly longer. In addition, the duration of the 0.5% levobupivacaine sensory block was determined as statistically significantly longer in Group II (190.00 ± 24.63 mins) than in Group I (172.50 ± 24.16 mins). Taking the mean highest sensory block levels into consideration, when the number of segments involved had been compared, more segments had been seen to be involved in Group II and the sensory block regression times per segment had been shorter. The heating of 0.5% levobupivacaine to 37°C provided a higher sensory block which lasted longer.

In conclusion, it can be said that the use of 0.5% levobupivacaine solution heated to 37°C not only provides a higher level of sensory block of a more predictable level, even though the regression time per segment is shorter, but also a longer-lasting sensory block. Given the times obtained in this study to reach the $T_{10}$ level of the sensory block, a more rapid start to the motor block is a result which can be expected.

The time taken to the start of the motor block in this study was determined as mean 11.43 ± 3.52 min in Group II and 18.23 ± 5.27 min in Group I. In addition the 10-minute Bromage score was found to be 3 in Group II and 1 in Group I. These differences between the groups were statistically significant. The time of the Bromage score regression from 3 to 2 was determined as 156.83 ± 32.60 min in Group II and 142.17 ± 28.03 min in Group I. The difference between the groups was found to be statistically significant.

As 0.5% levobupivacaine at 37°C became mildly hypobaric, it prolonged sensory block regression and motor block regression and this change in the baricity is thought to arise more from the spread of cephalin than the block.

In terms of haemodynamic changes in the current study, a reduction of a statistically significant level was determined in Group II compared to Group I. The reductions seen in the blood pressures of Group II can be explained by this group more rapidly reaching the block and having higher levels of sensory block. The drop in blood pressure values in both groups compared to the baseline values is thought to be associated with the drop in peripheral vascular resistance with spinal anaesthesia.

No statistically significant difference was determined between the groups in terms of saturation ($SpO_2$) measurements. The $SpO_2$ values did not fall below 93% in any case of the current study. This is thought to have been affected by the administration of oxygen via a face mask following the intrathecal application of local anaesthetic solution to the patients in the current study. Manara et al. emphasised the need for oxygen support for patients using sedative medication during routine spinal anaesthesia [23].

No statistically significant difference was determined between the groups of the current study in terms of the side effects of bradycardia, nausea, and vomiting. While a fall in SBP was determined in 4 patients of Group II who required ephedrine, no patient required ephedrine in Group I. This may be explained by Group II having reached higher levels of sensory block. In 1 patient of Group II who required atropine, a fall in HR was determined and in 2 patients of Group I who required atropine the fall in HR was determined as 48/min. The histories of the room temperature group patients who received atropine revealed preoperative HR measurements of approximately 50–55/min. No statistically significant difference was determined between the groups in respect of ephedrine and atropine use.

No difference was determined between the groups in this study in terms of patient and patient and surgeon satisfaction.

Similar results have been obtained to those of the current study; the effects on sensory block, motor block, and haemodynamics of subarachnoid space application of bupivacaine solution at different temperatures [7–9, 18]. In vitro studies showing the effects on density of different temperatures of local anaesthetic solution have features supporting the results obtained in the current study [1–6].
5. Conclusion

Time necessary for synchronisation of temperature within the CSF, the temperature of 0.5% levobupivacaine solution, is a significant factor in the determination of the sensory spread. It is easy to predict the analgesia levels when levobupivacaine solution preheated to 37°C is used. When a high level, long-lasting sensory block is required, the use of 0.5% levobupivacaine solution heated to 37°C is an attractive alternative method.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

Clinical Study

The Effectiveness of Preemptive Thoracic Epidural Analgesia in Thoracic Surgery

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Background. The aim of this study is to investigate the effectiveness of preemptive thoracic epidural analgesia (TEA) comparing conventional postoperative epidural analgesia on thoracotomy. Material and Methods. Forty-four patients were randomized in to two groups (preemptive: Group P, control: Group C). Epidural catheter was inserted in all patients preoperatively. In Group P, epidural analgesic solution was administered as a bolus before the surgical incision and was continued until the end of the surgery. Postoperative patient controlled epidural analgesia infusion pumps were prepared for all patients. Respiratory rates (RR) were recorded. Patient's analgesia was evaluated with visual analog scale at rest (VASr) and coughing (VASc). Number of patient's demands from the pump, pump's delivery, and additional analgesic requirement were also recorded. Results. RR in Group C was higher than in Group P at postoperative 1st and 2nd hours. Both VASr and VASc scores in Group P were lower than in Group C at postoperative 1st, 2nd, and 4th hours. Patient's demand and pump's delivery count for bolus dose in Group P were lower than in Group C in all measurement times. Total analgesic requirements on postoperative 1st and 24th hours in Group P were lower than in Group C. Conclusion. We consider that preemptive TEA may offer better analgesia after thoracotomy.

1. Introduction

Postoperative pain is one of the most important factors affecting the patient's morbidity. Thoracotomy is considered as one of the most severe acute postoperative painful surgeries [1]. Acute pain in these procedures can lead to respiratory and cardiovascular complications [2–4]. Coughing and clearance of secretion can be impaired after thoracotomy in patients with inadequate analgesia. This condition may prolong hospital stay and delay discharge from hospital with increase of the cost. For this reason different analgesic methods such as thoracic epidural analgesia (TEA), paravertebral blocks, and systemic analgesic can be used considered for this purpose. TEA is often regarded as to be the gold standard [5]. It was demonstrated that TEA provided better analgesia than conventional analgesia models in postthoracotomy pain [6–8]. Suitable planned TEA decreases postoperative morbidity and mortality providing optimal analgesia without respiratory insufficiency [9].

Also preemptive analgesia is a concept that a pain therapy is more effective if given before the surgical incision and noxious stimulus [10, 11]. It is thought to decrease the incidence of hyperalgesia and allodynia by decreasing the altered central sensory processing [12]. Therefore, systemic opioid-nonnopoiid analgesic use (iv, im), local anesthetic infiltration, and epidural or spinal local anesthetic administration have been used for preemptive analgesia [11, 13, 14].

The aim of this study is to find out whether preoperative initiation of epidural analgesia is superior compared to postoperative initiation on postthoracotomy pain.

2. Material and Methods

After obtaining the ethics committee approval and patient informed consent 44 patients between the ages of 18 and 65 with ASA I–III risk group have been taken in this study. Sealed envelope method was used for randomization.
and the patients undergoing elective unilateral thoracotomy operation were divided into two groups (preemptive: Group P, n = 22 and control: Group C, n = 22). Patients with ASA score of IV or more, body mass index 30 kg/m² or more, and severe renal, hepatic, or neurologic diseases and those using opioid or systemic analgesic preoperatively were excluded from the study.

All patients were administered midazolam 3 mg intramuscularly 30 min before the operation for sedation. In the operating room, electrocardiography, peripheral arterial oxygen saturation, and invasive arterial blood pressure were monitored. After the skin disinfection and lidocaine 20 mg administration for local anesthesia, 18G epidural catheter was inserted at T₅₋₈ intervertebral spaces in lateral decubitus position. Propofol (1.5–2.5 mg/kg) and fentanyl (2 μg/kg) were used intravenously for induc- tion anesthesia. After the administration of 0.15 mg/kg of cisatracurium, patients were intubated with double lumen tubes. For anesthesia maintenance, total intravenous anesthesia. After the administration of 0.15 mg/kg of cisatracurium, patients were intubated with double lumen tubes. For anesthesia maintenance, total intravenous anes-

The solution contained 0.1% levobupivacaine and 2 mg/mL fentanyl. For patients in preemptive group (Group P) 0.1 mL/kg of bolus standard epidural solution was administered 20 min before surgical incision via epidural catheter. Epidural infusion with 10 mL/h of the same solution was started 45 min after the bolus dose. And it was continued during the operation via epidural catheter. In patients in control group (Group C) equal volume of serum physiologic was administered as a bolus and infusion via epidural catheter during the operation. 0.1 mL/kg of standard epidural solution (0.1% levobupivacaine, 2 μg/mL fentanyl) was administered as a bolus via epidural catheter 20 min before the patient woke up.

After the patients were extubated and all of the drug infusions were discontinued, all patients were transferred to postanesthesia care unit for 24 hours under constant monitoring and clinical observation. Patient controlled epidural analgesia (PCEA) infusor (Abbott Laboratories) was performed on all patients. The PCEA pumps were set as a 5 mL/h of infusion, 3 mL of bolus dose, and 30 min of lock out time. Patient’s analgesia was evaluated with visual analog scale (VAS) (0, no pain at all; 10, worst imaginable pain). If the VAS score at rest was 4 or more tramadol 50 mg, as an additional analgesic, was administered intramuscularly.

VAS score at rest (VASr) and on coughing (VASC) and demand and delivery count of PCEA infusor were independently measured at postoperative 1st, 2nd, 4th, 6th, 12th, and 24th hours by a trained physician blinded to the randomization. Total tramadol requirements at postoperative 1st and 24th hour were recorded. The incidence of side effects such as nausea, vomiting, and pruritus was also recorded. Mean arterial pressure (MAP), heart rate (HR), and respiratory rate (RR) were measured at the same time periods. Hypotension was defined as a decrease in mean arterial pressure below 60 mmHg lasting at least 30 min and bradypnoea was defined as a respiratory rate <10 bpm. It was planned that the patient who developed hypotension or bradypnoea was treated and excluded from the study.

2.1. Statistical Analysis. Data were presented in the form of mean ± SD. All statistical analyses were carried out using SPSS statistical software (SPSS for windows, version 14.0). The Kolmogorov-Smirnov test was used to determine normality and homogeneity of data distribution. Parametric data (age, blood pressure, and OLV time) were compared using one-way analysis of variation (ANOVA). Nonparametric data were compared using the Kruskal-Wallis test. Mann-Whitney U test was for pain scores.

3. Results

There were no significant differences between the groups with respect to age, sex, ASA score, and surgery time (Table 1). Although MAP and HR were insignificant in comparison of the groups, RR in Group C was higher than in Group P at postoperative 1st and 2nd hours (postoperative 1st hour: 21.05±3.72, 18.25±3.64, postoperative 2nd hour: 20.45±3.41, 18.35 ± 2.83, resp.) (P < 0.05) (Table 2).

Data on postoperative pain at rest (VASr) and coughing (VASC) are shown in Tables 3 and 4. Both VASr and VASC scores in Group P were lower than in Group C at postoperative 1st, 2nd, and 4th hours (P < 0.01) (Tables 3 and 4).

When PCEA pump was examined, patient’s demand and pump’s delivery count for bolus dose in Group P were lower than in Group C on all measurement times (P < 0.01) (Figures 1 and 2).

When the additional analgesic requirement was compared, total tramadol amount on postoperative 1st and 24th hours in Group P was lower than in Group C (postoperative 1st hour: 17.5 ± 14.4, 45.0 ± 22.3, postoperative 24th hour: 75.0 ± 63.8, 130.0 ± 89.4, resp.) (P < 0.01 and P < 0.05, resp.) (Figure 3).

There were no differences between the groups with respect to side effects.

4. Discussion

This study showed that preincisional epidural initiation provided better analgesia than postoperative application for postthoracotomy pain. Pain score at rest and coughing were lower with preincisional initiation, especially in early postoperative period. Decreased number of patient’s demand from PCEA pump and pump’s delivery to the patients
Table 2: Mean arterial pressure (MAP; mmHg), heart rate (HR; beat/min), and respiratory rate (RR; count/min).

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group P</th>
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<tbody>
<tr>
<td></td>
<td>MAP (±SD)</td>
<td>HR (±SD)</td>
</tr>
<tr>
<td>Postoperative 1st hour</td>
<td>67.35 ± 12.30</td>
<td>87.40 ± 19.30</td>
</tr>
<tr>
<td>Postoperative 2nd hour</td>
<td>66.25 ± 11.30</td>
<td>86.45 ± 16.40</td>
</tr>
<tr>
<td>Postoperative 4th hour</td>
<td>66.12 ± 13.90</td>
<td>84.00 ± 13.60</td>
</tr>
<tr>
<td>Postoperative 6th hour</td>
<td>68.15 ± 12.86</td>
<td>83.05 ± 11.82</td>
</tr>
<tr>
<td>Postoperative 12th hour</td>
<td>66.12 ± 13.90</td>
<td>84.00 ± 13.60</td>
</tr>
<tr>
<td>Postoperative 24th hour</td>
<td>67.10 ± 12.99</td>
<td>84.00 ± 13.39</td>
</tr>
</tbody>
</table>

*P < 0.05 when RR at 1st and 2nd postoperative hours in Group C was compared with those in Group P.

Table 3: Postoperative pain score at rest (VASr) (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group P</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.05 ± 2.18β</td>
<td>1.90 ± 1.21</td>
<td>0.002</td>
</tr>
<tr>
<td>Postoperative 2nd hour</td>
<td>3.45 ± 2.23α</td>
<td>1.40 ± 0.94</td>
<td>0.001</td>
</tr>
<tr>
<td>Postoperative 4th hour</td>
<td>2.60 ± 1.93*</td>
<td>1.20 ± 0.83</td>
<td>0.009</td>
</tr>
<tr>
<td>Postoperative 6th hour</td>
<td>1.45 ± 1.27</td>
<td>1.05 ± 1.63</td>
<td>0.134</td>
</tr>
<tr>
<td>Postoperative 12th hour</td>
<td>1.10 ± 1.37</td>
<td>0.50 ± 0.82</td>
<td>0.134</td>
</tr>
<tr>
<td>Postoperative 24th hour</td>
<td>0.75 ± 1.02</td>
<td>0.35 ± 0.81</td>
<td>0.192</td>
</tr>
</tbody>
</table>

β When VASr scores at 1st postoperative hour in Group C were compared with those in Group P.
α When VASr scores at 2nd postoperative hour in Group C were compared with those in Group P.
* When VASr scores at 4th postoperative hour in Group C were compared with those in Group P.

Figure 1: Patient’s demand count on PCEA pump when Group C is compared to Group P (∗: P = 0.013, †: P = 0.000, ‡: P = 0.002, #: P = 0.001, α: P = 0.000, and β: P = 0.000).

Figure 2: Pump’s delivery count on PCEA pump when Group C is compared to Group P (∗: P = 0.013, †: P = 0.000, ‡: P = 0.002, #: P = 0.001, α: P = 0.000, and β: P = 0.000).

Previous studies were carried out to find out the benefit of preemptive analgesia. Bong et al. [1] stated that the effectiveness of preemptive epidural analgesia is more clear in thoracotomy surgery than in other surgical procedures. It was stated that thoracotomy produces excessive noxious stimuli caused by central sensitization [15–17]. Hence we carried out this study in patients undergoing thoracic surgery to demonstrate the effectiveness of preemptive epidural analgesia.

Yegin et al. [18] investigated the effectiveness of pre- and postoperative epidural analgesia versus postoperative epidural analgesia in thoracic surgery. They administered bupivacaine and fentanyl as a bolus to intervention group preoperatively. PCEA was applied to each group with the same protocol and VAS scores were recorded postoperatively. They found better analgesia with the preoperative initiation of epidural analgesia. Their findings were similar to our results.
Table 4: Postoperative pain score at coughing (VASc) (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group P</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative 1st hour</td>
<td>4.95 ± 2.01†</td>
<td>3.15 ± 1.22</td>
<td>0.007</td>
</tr>
<tr>
<td>Postoperative 2nd hour</td>
<td>4.40 ± 2.08a</td>
<td>2.55 ± 1.14</td>
<td>0.004</td>
</tr>
<tr>
<td>Postoperative 4th hour</td>
<td>3.50 ± 1.76*</td>
<td>2.20 ± 0.95</td>
<td>0.009</td>
</tr>
<tr>
<td>Postoperative 6th hour</td>
<td>2.55 ± 1.31</td>
<td>2.10 ± 1.48</td>
<td>0.192</td>
</tr>
<tr>
<td>Postoperative 12th hour</td>
<td>2.20 ± 1.54</td>
<td>1.40 ± 0.94</td>
<td>0.108</td>
</tr>
<tr>
<td>Postoperative 24th hour</td>
<td>1.60 ± 1.18</td>
<td>1.05 ± 1.05</td>
<td>0.121</td>
</tr>
</tbody>
</table>

† When VASr scores at 1st postoperative hour in Group C were compared with those in Group P.
a When VASr scores at 2nd postoperative hour in Group C were compared with those in Group P.
* When VASr scores at 4th postoperative hour in Group C were compared with those in Group P.

Amr et al. [19] carried out a study to find out the effects of preincisional epidural application on pulmonary and endocrine system besides pain. They showed significant improvement in pulmonary functions along with better analgesia in preincisional group as compared with the postoperative group. However, the oxygenation, cortisol, or glucose levels were found insignificant and concluded that, although preemptive analgesia provided better analgesia and preserved pulmonary functions, it had no effect on stress response and these findings were not enough to conclude a clinical significant difference. The amount of epidural local anesthetic may lead to this indifference between the groups on stress response. Their patient’s VAS score at rest and coughing was relatively high (VAS > 3 in early postoperative period). Motor block is most fearful complication of thoracic epidural analgesia with local anesthetic. As they used bupivacaine, powerful motor blocking agent, they could not administer more high dose epidural local anesthetic. If better analgesia was provided, the positive effect on stress response might be demonstrated.

Ideal local anesthetic agent for thoracic epidural analgesia must have fast and long acting analgesia, lower motor block and hemodynamic side effects, and higher toxic dose limit [20]. Levobupivacaine, S-enantiomer of racemic bupivacaine, is along acting local anesthetic that caused less neuro- and cardiotoxic side effects than other local anesthetics [9, 21]. These properties of levobupivacaine enable it to be used in higher doses safely to achieve sufficient analgesia. Thus, we chose levobupivacaine and achieved required analgesia. Mendola et al. [22] used 10 mg/h levobupivacaine via epidural catheter postoperatively for postthoracotomy pain and stated that this application can provide sufficient analgesia. However, they administered paracetamol 1.5 gr and ketorolac 60 mg daily to patients. If the epidural levobupivacaine initiated preoperatively, these analgesics were not needed.

Chronic postthoracotomy pain is recurred or persisted along the thoracotomy scar more than two months after surgery [23]. It was stated that acute pain after thoracotomy was related to chronic postthoracotomy pain [17]. Thus, studies were carried out to demonstrate the preventive effects of preemptive epidural analgesia on chronic postthoracotomy pain [24–27]. Şentürk et al. [25] compared the effects of TEA with and without preoperative initiation on postthoracotomy pain. At the end of their study, they stated that TEA with preoperative initiation can prevent acute and long term thoracotomy pain. Similarly, Ochroch et al. [26] carried out a study, but with higher dose of bupivacaine, to investigate the effectiveness of preemptive TEA. They concluded a benefit of preemptive analgesia.

On the other hand, studies show that clinical effectiveness of preemptive analgesia is controversial [28–30]. Neustein et al. [27] compared the pre- versus postoperative initiated TEA using bupivacaine. They found that preemptive TEA provided better analgesia until postoperative 6th hour and VAS scores after 6th hour which is insignificant. We also found similar findings. But their VAS scores in both pre- and postoperative initiation groups were higher than ours. They used only preoperative bolus of bupivacaine, but not infusion. Higher VAS scores may be explained by insufficient analgesia.

Although our findings encourage us to use preemptive TEA to provide sufficient analgesia after thoracotomy there were some limitations in our study. We record VAS scores only until postoperative 24th hour. And we did not investigate the effects of TEA on pulmonary functions and stress...
response in more detail. If we had evaluated these parameters, this study may be more powerful.

In conclusion we consider that preemptive TEA may offer better analgesia after thoracic surgery. However, further studies with more patients are needed to demonstrate the benefits of preemptive epidural analgesia providing better analgesia with less side effects and positive outcomes from stress response.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


Clinical Study

Peri- and Postanalgesic Properties of Lidokain, Lornoxicam, and Nitroglycerine Combination at Intravenous Regional Anesthesia

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Background. This study was conducted to compare and evaluate the effect of adding lornoxicam or nitroglycerine as adjuncts to lidocaine in intravenous regional anesthesia (IVRA). Methods. 60 patients were randomly separated into three groups, lidocaine group (group L), lidocaine + lornoxicam group (group LL), and lidocaine + lornoxicam + transdermal nitroglycerine group (group LL-N). Hemodynamic parameters, sensory and motor blocks onset, and recovery times were recorded. Analgesic consumption for tourniquet pain and postoperative period were recorded. Results. Sensory block onset times and motor block onset times were shorter in the LL-N and LL groups compared with group L. Sensory block recovery time and motor block recovery time were prolonged in the LL and LL-N groups compared with group L. The amount of fentanyl required for tourniquet pain was less in group LL and group LL-N compared with group L. VAS scores of tourniquet pain were higher in group L compared with the other study groups. Postoperative VAS scores were higher for the first 4 hours in group L compared with the other study groups. Conclusion. The adjuvant drugs (lornoxicam or TNG) when added to lidocaine in IVRA were effective in improving the overall quality of anesthesia, reducing tourniquet pain, increasing tourniquet tolerance, and improving the postoperative analgesia.

1. Introduction

Intravenous regional anesthesia (IVRA) is widely recommended and applied in patients undergoing ambulatory procedures. Various additives have been used with local anesthetic agents to improve block quality, reduce tourniquet pain, and prolong postdeflation analgesia [1]. The potential intraoperative benefit of nonsteroidal anti-inflammatory drugs (NSAIDs) added to local anesthetic agents have been demonstrated at several studies [2, 3]. Lornoxicam is a new NSAID of the oxicam class which is available in oral and parenteral forms. It is a nonopioid analgesic as effective as morphine, tramadol, and meperidine and produces less adverse effects than others [4]. Transdermal nitroglycerine (TNG), nitric oxide generator, helps in distribution of local anesthetic agents to neuron trunks by vasodilatation and also it has been demonstrated that, when transdermal nitroglicerine is used with other drugs, analgesic effect is increased. Nitric oxide and NSAID drug combinations are produced. It is called (NONSAID) for reducing adverse effects of NSAID drugs which are caused by COX enzyme inhibition [5–9]. This study was designed to compare and evaluate the effect of adding lornoxicam or both lornoxicam and TNG as adjuncts to lidocaine for IVRA.
2. Methods

With hospital ethics committee approval and informed written consent, we recruited 60 non-premedicated ASA physical status I-II 18- to 40-year-old patients undergoing elective hand, wrist, and forearm surgery procedures. Patients with Raynaud's disease, sickle cell anemia, and history of drug allergies were excluded from the study.

The study design was randomized and double-blinded. An anesthesia assistant who was blinded to study prepared identical syringes containing each drug according to randomisation list. At premedication room, two cannulae were placed; 22-gauge cannula was placed in dorsal vein of operative hand for applying study drugs; and other cannulae was placed in the opposite hand for fluid 5% ringer lactate infusion administration.

Monitoring includes measurement of arterial blood pressure (mean arterial pressure (MAP)), heart rate (HR), and saturation of peripheral oxygen (SpO2) (Taema Artema MM206, Artema Medical AB Sundbyberg, Sweden). After application of standard monitoring, operative arm was elevated for two minutes and was then exsanguinated with an Esmarch bandage from distal to proximal. We placed a pneumatic tourniquet which has double cuff around the upper arm. Proximal cuff was inflated to 250 mmHg, and distal tourniquet was not inflated. Circulatory isolation of the arm was verified by inspection, absence of radial pulse, and loss of pulse oximetry reading in the ipsilateral index finger. The tourniquet period was from the time at which the distal cuff was inflated to the time the patient experienced pain.

The syringes contained 3 mg/kg lidocaine 2% (Aritmal, TEMS, Istanbul, Turkey) diluted with saline to a total volume of 40 mL in all groups for IVRA.

Patients were randomized to three groups with 20 patients in each.

Group I (Group L) (Lidocaine Group). 3 mg/kg lidocaine 2% (Aritmal, TEMS, Istanbul, Turkey) was diluted with saline to a total volume of 40 mL. Two hours before the operation, empty TNG flaster (Nitroderm, TTS flaster, Novartis) was placed on the hand at which the operation would be performed.

Group II (Group LL) (Lidocaine + Lornoxicam Group). 3 mg/kg lidocaine 2% (Aritmal, TEMS, Istanbul, Turkey) was diluted with saline to a total volume of 40 mL. Two hours before the operation, empty TNG flaster (Nitroderm, TTS flaster, Novartis) was placed on the hand at which the operation would be performed.

Group III (Group LL-N) (Lidocaine + Lornoxicam + TNG Group). 3 mg/kg lidocaine 2% (Aritmal, TEMS, Istanbul, Turkey) was diluted with saline to a total volume of 40 mL and also 8 mg lornoxicam (Xefo, Abdi Ibrahim, Turkey) was added to the solution. Two hours before the operation, TNG flaster which contains 5 mg nitroglycerine (Nitroderm, TTS flaster, Novartis) was placed at the surgical site.

The study solutions were injected over 90 seconds by an anesthesiologist blinded to the study drugs.

After IVRA was achieved, sensory block was assessed by a pinprick testing performed with a 22-gauge short-beveled needle. Patient response was evaluated in the dermatomal sensory distribution of ulnar, median, and radial nerves. Sensory block onset time was noted as the time elapsed from injection of study drug to sensory block achieved in all dermatomes.

Motor function was assessed by asking the subjects to flex and extend his/her wrist and fingers, and complete motor block was noted when no voluntary movement was possible. Motor block onset time was the time elapsed from injection of the study drug to complete motor block.

After sensorial and motor blocks were assessed at all dermatomes, distal cuff was inflated to 250 mmHg, and proximal cuff was deflated after taking out TNG patch. Pain due to the tourniquet was assessed with a 10 cm visual analogue scale (VAS) (0 = no pain and 10 cm = worst pain imaginable). HR, MAP, SPO2, and VAS were monitored and recorded before and after the application of the tourniquet and 1, 5, 15, 30, and 45 minutes after the injection of local anesthetic solution.

If the patient reported VAS > 3 during the surgery, 1 µg/kg IV fentanyl (fentanyl citrate; Abbott, North Chicago, IL) was given. Total fentanyl requirement (dose and time) was recorded.

During the surgery time, 4 mg IV ondansetron hydrochloride (Zofran, GlaxoSmithKline) was given for nausea and vomiting, 5 mg IV ephedrine was given for hypotension (systolic arterial blood pressure < 90 mmHg or 50 mmHg lower than the normal value), and 0.5 mg IV atropine was given for bradycardia (HR < 50/min). All of these complications were also recorded with respect to time.

After the surgery, the anesthesiologist, who did not know what medication was given by TNG patch and injection, was asked to qualify the anesthetic conditions according to the following numeric scale.

At the end of the operation the 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.

Unsuccessful (1) = patient given general anesthesia.

At the end of the surgery, the surgeon, who was blind to patient group, was asked to score operative conditions such as disturbing movement of arm and excessive bleeding according to the following numeric scale [10]:

0 = unsuccessful;

1 = poor;

2 = acceptable;

3 = good;

4 = excellent.
The tourniquet was not deflated before 30 minutes and was not inflated more than 2 hours. At the end of surgery, the tourniquet deflation was performed by the cyclic deflation technique. After tourniquet deflation, sensory recovery time (the time elapsed after tourniquet deflation up to recovery of pain in all innervated areas determined by pinprick test done every 30 seconds) was noted. Motor block recovery time (the time elapsed after tourniquet deflation up to movement of fingers) was noted. First analgesic requirement time (the time elapsed after tourniquet release to the first patient request of analgesic) was also noted.

Nausea, vomiting, skin reactions, dizziness, tinnitus, tachycardia, bradycardia, hypotension, and hypertension were noted until discharge from the recovery room and at the end of the 24 h postoperative observation period.

IM diclofenac (Voltaren; Ciba-Geigy, Istanbul, Turkey) 75 mg was given to patients with a VAS > 3 at postoperative first 8 hours and total diclofenac requirements (time and amount) were recorded by a blinded anesthesia resident. Patients were instructed to take one peroral paracetamol (Parol tablet 500 mg; Atabay) tablet at postoperative 8–24 hours required for a VAS > 3 while at home. All the patients were called by telephone the day after surgery by a blinded observer. The time from tourniquet deflation until the patient first required analgesic, diclofenac im or/and peroral paracetamol, was noted at the first postoperative 24-hour period.

2.1. Statistical Analysis. The statistical evaluation was done using SPSS 17.0 for Eindows (SPSS Inc., Chicago, IL, USA). Initial sample size estimation showed that approximately 18 patients were needed in each group to detect a clinically relevant reduction of fentanyl consumption by 25% and also approximately 50% clinically significant changes of the sensory block onset and recovery times with a power of 80% and a level of significance of 5%. Independent samples t-test was used for evaluation of the demographic data, hemodynamic data, the time of sensory and motor block onset and the recovery time, duration of surgery and tourniquet, initial time of tourniquet pain, VAS scores, postoperative first analgesic requirement time, and intraoperative and postoperative analgesic use. Mann-Whitney U test was used for intraoperative and postoperative quality of anesthesia. Level of significance was determined at $P > 0.05$ for no statistically significant difference and at $P < 0.05$ for significant difference.

3. Results

Demographic data of the groups were similar to mean age, weight, height, and sex ratio (Table 1). All patients were able to complete the study, and there were no exclusions in data analysis. There were no statistical differences between groups’ duration of surgery and tourniquet time (Table 1). Sensory block onset times were shorter in the LL-N (3.1 ± 0.33 minutes) and LL (5.10 ± 0.38 minutes) groups compared with group L (6.2 ± 0.33 minute) ($P < 0.0001$) and motor block onset times were shorter in the group LL (8.4 ± 1.6 minutes) and group LL-N (4.7 ± 1.2 minutes) compared with group L (11.2 ± 1.5 minutes) ($P < 0.0001$). Sensory block recovery time was prolonged in the LL (7.6 ± 0.72 minutes) and LL-N (8.9 ± 0.77 minutes) groups compared with group L (3.1 ± 0.53 minutes) ($P = 0.001$). Motor block recovery time was prolonged in the LL (8.4 ± 1.4 minutes) and LL-N (79 ± 1.2 minutes) groups compared with group L (71 ± 1.2 minutes) ($P = 0.0014$ and 0.023, resp.) (Tables 2 and 3). The number of patients who need additional fentanyl requirements were significantly more in group L than the other two groups ($P = 0.047$), but amount of fentanyl required for tourniquet

### Table 1: Patients demographics data, duration of tourniquet, and surgery time.

<table>
<thead>
<tr>
<th></th>
<th>Group L ($n = 20$)</th>
<th>Group LL ($n = 20$)</th>
<th>Group LL-N ($n = 20$)</th>
<th>$p_1$</th>
<th>$p_2$</th>
<th>$p_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.70 ± 3.26</td>
<td>55.70 ± 2.38</td>
<td>51.30 ± 3.17</td>
<td>0.063</td>
<td>0.43</td>
<td>0.28</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>14/16</td>
<td>16/14</td>
<td>17/13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.20 ± 1.96</td>
<td>76.70 ± 2.4</td>
<td>73.20 ± 3.12</td>
<td>0.88</td>
<td>0.42</td>
<td>0.401</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 ± 7</td>
<td>162 ± 6</td>
<td>161 ± 5</td>
<td>0.13</td>
<td>0.15</td>
<td>0.23</td>
</tr>
<tr>
<td>Tourniquet time (min)</td>
<td>43.00 ± 4.73</td>
<td>39.30 ± 3.51</td>
<td>39.50 ± 3.86</td>
<td>0.53</td>
<td>0.57</td>
<td>0.97</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>35.10 ± 4.00</td>
<td>33.80 ± 3.60</td>
<td>34.50 ± 3.58</td>
<td>0.81</td>
<td>0.91</td>
<td>0.89</td>
</tr>
</tbody>
</table>

(Values are mean ± SD); $p_1$: comparison of groups L and LL; $p_2$: comparison of groups L and LL-N; and $p_3$: comparison of groups LL and LL-N.

### Table 2: Onset and recovery times of sensory and motor blocks (min).

<table>
<thead>
<tr>
<th></th>
<th>Group L ($n = 20$)</th>
<th>Group LL ($n = 20$)</th>
<th>Group LL-N ($n = 20$)</th>
<th>$p_1$</th>
<th>$p_2$</th>
<th>$p_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory block onset time (min)</td>
<td>6.20 ± 0.33</td>
<td>5.10 ± 0.38</td>
<td>3.40 ± 0.31</td>
<td>0.041</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>Sensory block recovery time (min)</td>
<td>3.10 ± 0.53</td>
<td>7.60 ± 0.72</td>
<td>8.90 ± 0.77</td>
<td>0.001</td>
<td>0.001</td>
<td>0.23</td>
</tr>
<tr>
<td>Motor block on set time (min)</td>
<td>11.3 ± 1.5</td>
<td>8.4 ± 1.6</td>
<td>4.7 ± 0.82</td>
<td>0.67</td>
<td>0.25</td>
<td>0.15</td>
</tr>
<tr>
<td>Motor block recovery time (min)</td>
<td>7.1 ± 1.2</td>
<td>8.4 ± 1.4</td>
<td>7.9 ± 1.2</td>
<td>0.001</td>
<td>0.001</td>
<td>0.1</td>
</tr>
</tbody>
</table>

(Values are mean ± SD); $p_1$: comparison of groups L and LL; $p_2$: comparison of groups L and LL-N; and $p_3$: comparison of groups LL and LL-N.
Intravenous regional anesthesia (IVRA) is a simple, common, and a reliable method which provides adequate anesthesia and muscle relaxation at short operative procedures of extremity surgery. Lidocaine is the most commonly chosen local anesthetic for IVRA. But, there are well-known limitations to this local anesthetic especially at prolonged surgery and postoperative period.

Various additives have been used with local anesthetics to improve block quality, reduce tourniquet pain, and prolong postdeflation analgesia and varying results with the possibility of additional complications have occurred. Additives used were opioids (fentanyl, meperidine, morphine, and sufentanil), tramadol, NSAIDs (ketorolac, tenoxicam, lornoxicam, and acetylsalicylate), clonidine, dexametomidine, nitroglycerine, muscle relaxants (atracurium, pancuronium, and mivacurium), alkalinization with sodium bicarbonate and potassium [1, 10–14].

NSAIDs inhibit the production of prostaglandins from arachidonic acid in phospholipid membranes. The result is decreased afferent nociceptive signal arising from the site of surgery and also they act at peripheral nociceptors, perhaps by interfering with the synthesis and activity of pain mediators derived from arachidonic acid, and can supplement postoperative pain relief. NSAIDs as a part of IVRA have longer analgesic benefit than the same dose parenterally administered [1, 15].

Lornoxicam (chlortenoxicam) is a nonselective NSAID of the oxicam class, with analgesic, anti-inflammatory, and antipyretic effects. It is a highly potent short acting analgesic agent. It is available in oral and parenteral forms. It is separated from established oxicams by a relatively short elimination half-life (3 to 5 hours); this may be suggested as advantageous for use in postoperative period and also advantageous due to tolerability. In particular, it has a tolerability profile characteristics of NSAIDs, with gastrointestinal disturbances (pain, dyspepsia, nausea, and vomiting) being the most remarkable events. Lornoxicam is highly effective in both relieving postoperative pain and reducing the need for rescue analgesics following different surgical procedures [4, 15–23]. The beneficial effect of lornoxicam on postoperative pain relief in our study was clinically evident by lower pain scores and longer time to diclofenac rescue request with a reduction in the first 8- and 24-hour analgesic consumption, but it is not statistically evident [19].

Sen and colleagues show that addition of NSAID (lornoxicam) to lidocaine for IVRA shortens the onset of sensory and motor block, decreases tourniquet pain, and improves postoperative analgesia without causing any side effects. In another study, they add NSAID (ketorolac) to lidocaine for IVRA and they conclude that ketorolac improves IVRA with lidocaine in terms of controlling intraoperative tourniquet pain by diminishing postoperative pain [16]. NSAIDs as a part of IVRA have longer analgesic benefit than the same dose parenterally administered [1]. We have

### Table 3: Initial time of tourniquet pain (min).

<table>
<thead>
<tr>
<th>Group</th>
<th>(n = 20)</th>
<th>Group LL (n = 20)</th>
<th>Group LL-N (n = 20)</th>
<th>p1</th>
<th>p2</th>
<th>p3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial time of tourniquet pain (min)</td>
<td>15.80 ± 5.41</td>
<td>7.00 ± 4.90</td>
<td>3.00 ± 3.00</td>
<td>0.24</td>
<td>0.009</td>
<td>0.17</td>
</tr>
</tbody>
</table>

(Values are mean ± SD); p1: comparison of groups L and LL; p2: comparison of groups L and LL-N; and p3: comparison of groups LL and LL-N.

### Table 4: Total amount of fentanyl, diclofenac, and paracetamol requirement (μg).

<table>
<thead>
<tr>
<th>Group</th>
<th>(n = 20)</th>
<th>Group LL (n = 20)</th>
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<th>p1</th>
<th>p2</th>
<th>p3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total amount of fentanyl requirement (μg)</td>
<td>51 ± 61</td>
<td>15 ± 32</td>
<td>7 ± 22</td>
<td>0.047</td>
<td>0.017</td>
<td>0.15</td>
</tr>
<tr>
<td>Diclofenac requirement (mg)—postoperative first 8 hour</td>
<td>60 ± 31</td>
<td>37 ± 39</td>
<td>45 ± 38</td>
<td>0.11</td>
<td>0.35</td>
<td>0.67</td>
</tr>
<tr>
<td>Paracetamol requirement (mg)—postoperative 24 hours</td>
<td>850 ± 579</td>
<td>450 ± 497</td>
<td>100 ± 210</td>
<td>0.17</td>
<td>0.001</td>
<td>0.55</td>
</tr>
</tbody>
</table>

(Values are mean ± SD); p1: comparison of groups L and LL; p2: comparison of groups L and LL-N; and p3: comparison of groups LL and LL-N.

4. Discussion

The main result of our study revealed that the addition of both lornoxicam and nitroglycerin during IVRA improved speed of sensory and motor block onset times, decreased tourniquet pain, improved quality of anesthesia, and decreased intraoperative and postoperative analgesic consumption without causing any side effects.

Intravenous regional anesthesia (IVRA) is a simple, common, and a reliable method which provides adequate anesthesia and muscle relaxation at short operative procedures of extremity surgery. Lidocaine is the most commonly chosen local anesthetic for IVRA. But, there are well-known limitations to this local anesthetic especially at prolonged surgery and postoperative period.

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<th>p2</th>
<th>p3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (beat/min)</td>
<td>MAP (mmHg)</td>
<td>HR (beat/min)</td>
<td>MAP (mmHg)</td>
<td>HR (beat/min)</td>
<td>MAP (mmHg)</td>
</tr>
<tr>
<td>Preop</td>
<td>72.80 ± 3.09</td>
<td>94.20 ± 6.07</td>
<td>72.50 ± 1.75</td>
<td>99.70 ± 6.36</td>
<td>86.50 ± 6.14</td>
<td>0.93</td>
</tr>
<tr>
<td>15 min</td>
<td>71.50 ± 3.58</td>
<td>88.90 ± 5.61</td>
<td>69.70 ± 1.64</td>
<td>96.30 ± 5.72</td>
<td>69.90 ± 2.61</td>
<td>0.65</td>
</tr>
<tr>
<td>30 min</td>
<td>68.50 ± 3.18</td>
<td>88.20 ± 4.01</td>
<td>67.90 ± 1.55</td>
<td>97.70 ± 4.20</td>
<td>70.10 ± 2.77</td>
<td>0.86</td>
</tr>
<tr>
<td>45 min</td>
<td>69.20 ± 2.56</td>
<td>88.80 ± 4.76</td>
<td>67.70 ± 1.01</td>
<td>97.30 ± 4.52</td>
<td>68.90 ± 2.93</td>
<td>0.59</td>
</tr>
</tbody>
</table>

(Values are mean ± SD); p1: comparison of groups L and LL; p2: comparison of groups L and LL-N; and p3: comparison of groups LL and LL-N.
tourniquet and postoperative pains, without any side effect on onset times of sensory and motor block and decreased the adding NTG to lidocaine in IVRA where it shortened the adjuvant to IVRA. Abbasivash et al. studied the effect of pain [8]. Lauretti et al. documented that transdermal NTG of transdermal glycerylnitrate in the treatment of shoulder pain conditions. Berrazueta et al. proved the analgesic action have demonstrated its analgesic effect in acute and chronic of transdermal lidocaine. It then spreads around the small nerves in vasculature and capillary plexus of the nerves, leading to a core-to-mantle (centrifugal) conduction block in the small veins surrounding the nerves and then into the skin, blocking their conduction. Several studies on NTG nerves involved. It then spreads around the small nerves in the skin, blocking their conduction. Several studies on NTG shows its analgesic effect as it is metabolized to effects compared to lornoxicam alone [16]. Our results seem to be similar to those of Abbasivashi et al. and Sen et al. Sensory and motor block onset times were statistically shorter in group LL-N than in group LL and group L. This could be explained by direct vasodilator effect of nitroglycerine that promotes distribution of lidocaine to nerves. There were also lower VAS scores for tourniquet pain and reduced paracetamol requirement time in group NTG. In our study, there was no significant difference in side effects between the three groups; this can be due to the fact that nitroglycerin produces antioxidative effect [27]. In that respect, the antioxidative effects of the drug might be particularly important for preventing gastrointestinal side effects. Transdermal nitroglycerin patch may, in fact, reduce gastric damage induced by parenteral administration of indomethacin [28]. It was also demonstrated that nitric oxide–releasing NSAIDs (NONSAID) can prevent gastrointestinal side effects in acute and chronic administration in animals. Sen et al. suggests that lornoxicam may cause gastrointestinal and renal side effects. Adding nitroglycerin to lornoxicam might prevent gastrointestinal and renal side effects compared to lornoxicam alone [16].

In conclusion, addition of lornoxicam or TNG to lidocaine in IVRA was effective in improving the overall quality of anesthesia, reducing tourniquet pain, increasing tourniquet tolerance, and improving the postoperative analgesia. The combination of lidocaine, lornoxicam, and TNG as an adjuvant produced faster onset of sensory and motor blockades in comparison to other groups. The underlying mechanisms are yet to be elucidated with more experimental studies.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.
References


