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The Effect of Adding Dexamethasone and dexketoprofen to lidocaine in anesthesia and postoperative analgesia as a regional intravenous anesthesia technique

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INTRODUCTION

Regional anesthesia is a widely used method because of more advantages compared to general anesthesia (1). Anesthesia is called Intravenous Regional Anesthesia (IVRA), which is created by giving a local anesthetic into the venous system of an extremity isolated from the systemic circulation by applying a tourniquet with a pressure above the systemic arterial pressure to the proximal part, eliminating the sensation of nerve conduction and pain (2). In patients undergoing upper extremity surgery; Intravenous regional anesthesia (IVRA) is a frequently preferred method due to its ease of administration, rapid onset of action and effective anesthesia, and short hospital stay (3).

Lidocaine and prilocaine are frequently preferred agents in IVRA. One of the major disadvantages of IVRA is that it has insufficient postoperative analgesic efficacy. Although it is tried to prevent unwanted systemic symptoms by decreasing the applied local anesthetic doses; these practices cause inadequate anesthesia (4). Many alternative drugs and methods are being studied in order to reduce unwanted systemic findings and extend the duration of anesthesia (5). For this purpose, after the detection of peripheral opioid receptors, morphine, fentanyl, tramadol, etc. Agents such as opioids, low-dose muscle relaxants, nonsteroidal anti-inflammatory drugs, clonidine to provide surgical muscle relaxation were added to local anesthetics, and alkalinization of local anesthetics was used in regional anesthesia to shorten the onset of local anesthetics and to prolong analgesia (6, 7). In this study, we planned to compare the sensory and motor block initation and end times, anesthesia quality, tourniquet tolerance, postoperative analgesia quality and side effects of adding dexketoprofen and dexamethasone to IVRA made with lidocaine.

MATERIALS and METHODS

The study was planned in 60 adult patients from ASA I-III group over the age of 18 who will undergo hand and wrist surgery with the approval of the hospital ethics committee and informed patient at the 1st Anesthesiology and Reanimation Clinic of the University of Health Sciences, Yıldırım Beyazıt Training and Research Hospital.

Cases contraindicated for IVRA application (presence of allergy to lidocaine, dexketoprofen and dexamethasone, thrombophlebitis and atherosclerotic vascular diseases, history of bronchial asthma, Raynoud's disease, arterio-venous fistula, scleroderma, sickle cell anemia, extensive burns to the

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operation site, laceration and infection, patients with myasthenia gravis, bleeding disorder, decompensated heart failure and digitalized patients, epilepsy, non-cooperative patients, sedentary and malnourished patients and those with liver dysfunction) and patients who did not accept the technique were excluded from the study.

All cases premedicated with 0.05 mg / kg i.m. midazolam (Dormicum, Roche) 30 minutes before the operation. Venous cannulation was performed with 22 gauge intravenous cannula on the dorsum of the hand, and infusion was started at a rate of 4-6 ml / kg / hour with 0.9% NaCl.

The demographic data of the patients who were taken to the operating table were recorded. Systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SPO2) by electrocardiography (ECG) and pulse oximetry were monitored (Drager infinity alpha).

The arm, which was planned to be operated, was first kept above the heart level for 3 minutes and the venous blood of the arm was drained by the effect of gravity. Then, the anemia process was completed by wrapping the Esmarch bandage tightly from distal to proximal. The proximal cuff of the double-cuffed tourniquet (VBM Medizintechnik, GMBH, Germany) was inflated to a pressure of 100 mmHg or 300 mmHg above the systolic arterial blood pressure measured from the same arm. Occlusion pressure was confirmed by the disappearance of the radial pulse.

The patients were randomly divided into 3 groups and Lidocaine was given to the 1st group (Group I) with regional anesthesia technique, while Lidocaine + Dexamethasone to the 2nd group (Group II) and Lidocaine + Dexamethasone + Dexketoprofen to the 3rd group (Group III) were planned.

GROUP I (n = 19): 3 mg / kg of 2% Lidocaine was completed to 40 ml with saline.

GROUP II (n = 19): 3 mg / kg 2% Lidocaine + 8 mg Dexamethasone was completed to 40 ml with saline.

GROUP III (n = 18): 3 mg / kg 2% Lidocaine + 8 mg Dexamethasone + 50 mg Dexketoprofen was completed to 40 ml with saline.

The solution prepared for each group was injected in 90 seconds by the anesthesiologist immediately after the proximal tourniquet was inflated from the vein cannulation on the dorsum of the hand on the side where the operation was planned. The time to occurrence of the sensory block from the end of the injection was determined every 30 seconds by performing a pinprick test with the help of a 22 G short needle in 6 regions determined in the dermatomes of the median, radial and ulnar nerves. In these dermatomes, when the sensation of pain was not detected in the pinprick test performed by inserting a needle, the sensory block initiation time was recorded. The time to occurrence of motor block was recorded as the time from drug injection until the patients could not move their fingers. After the sensory block was formed in all dermatomes, the distal tourniquet was inflated to a pressure of 300 mmHg and the operation was initiated by opening the proximal tourniquet.

Visual Analogue Scale (VAS) values were recorded before and immediately after the tourniquet, at 5, 10, 15, 20 and 40 minutes after the injection of the prepared solution. Assessment of tourniquet pain with VAS, which is a pain assessment scale between 0 and 10; The evaluation of sedation status was performed with the Ramsey Sedation Scale, which was evaluated with a score between 1 and 5; The evaluation of the degree of motor block was done with the Bromage Scale, which was evaluated with a score between 0 and 3; Anesthesia quality was performed with a numerical scale scored between 1 and

4. Side effects such as bradycardia, hypotension, diplopia, dizziness, nausea, vomiting, cyanosis and nystagmus that may develop during the operation were recorded. When hypotension developed (mean arterial pressure decreased by 25% compared to preoperative values) iv 5¬10 mg ephedrine, when bradycardia developed iv 0.5 mg atropine and when SpO2 was 91%, it was planned to be treated by giving oxygen through a face mask. Fentanyl (Fentanyl Citrate-Abbott) at a dose of 1 pgr / kg was planned for those with a VAS value of 3 and above.

A 5-point scale (Ramsey Sedation Scale) was used for sedation.

1= alert, cooperative

2= prone to sleep

3= sleeping but responding to audible stimulus

4= fits but has response to tactile stimulus

5= sleeping but has no response to any stimulus.

Numerical Scale was used to evaluate the quality of anesthesia.

Perfect (4): patient comfortable, no analgesic requirement.

Good (3): minor analgesic need

Medium (2): needs additional analgesic.

Unsuccessful (1): general anesthesia was started.

The degree of motor block was evaluated using the Bromage Scale.

0 = no paralysis at all.

1= can only move her elbow and hand. He cannot raise his arm straight.

2= Cannot bend elbow, only move hand.

3= Can't move wrist and thumb.

The tourniquet was not lowered 20 minutes before the anesthetic agent injection and was not allowed to stay for more than 2 hours. After the tourniquet was opened, the time until the return of pain sensation with pinprick test in radial, median and ulnar nerve dermatomes was recorded as the return time of sensory block. The time until the patient could move his fingers was recorded as the motor block return time. VAS values, sedation status and side effects were recorded at 1, 10, 2, and 4 hours after the tourniquet was opened. The time between the opening of the tourniquet and the first analgesic administration was accepted as the time of analgesia and the time of first analgesic administration was recorded. The total amount of analgesic taken in the first 24 hours was recorded. If he needed 500 mg paracetamol tablet as analgesic, he was recommended to take a maximum of 4 tablets in 24 hours.

Statistical analysis

The analysis of the data was performed using the SPSS (Statistical Package for Social Science) for Windows 11.5 package program. Whether the distribution of continuous variables was close to normal was examined using the Shapiro Wilk test. Descriptive statistics were presented as mcan ± Standard deviation or median (minimum-maximum) for continuous variables, and as number of cases and (%)

for categorical variables.

Whether there is a statistically significant difference between the groups in terms of age and body weight. One-way analysis of variance, starting and ending times of motor and sensory block, VAS, amount of Fentanyl consumed, first post-op analgesic intake time, total analgesic consumption, tourniquet VAS, Sedation score and the significance of the difference in terms of anesthesia quality scores was investigated with the Kruskal Wallis test. If the Kruskal Wallis test statistic result was found to be significant, the non-parametric multiple comparison test was used to identify the groups that caused a significant difference. Categorical variables were analyzed using Pearson's Chi-Square or Fisher's Exact-Result Chi-Square test. Whether there was a statistically significant difference between the repeated measurements within the groups was investigated with the Bonferroni Corrected Wilcoxon Sign test.

For $p < 0.05$, the results were considered statistically significant. Bonferroni Correction was made to control the Type I error in all possible multiple comparisons.

RESULTS

In our study, demographic characteristics of 56 cases who underwent IVRA are shown in Table I, and no statistical difference was observed between the groups in terms of age, weight, gender, ASA classification ($p > 0.05$) (Table 1).

Sensorial and Engine Block Evaluation

Sensorial Block Start and End Time:

No statistically significant difference was found between the groups in terms of onset of sensory block ($p > 0.05$) (Table 2).

Engine Block Start and End Time:

Motor block onset time of Group III was statistically significantly shorter than Group I and Group II (Table 2) ($p < 0.05$). There was no statistically significant difference between Group I and Group II (Table 2) ($p > 0.05$).

VAS Values of Groups:

No statistically significant difference was found between the groups in terms of VAS values in the perioperative period ($p > 0.006$). The difference between post-op 1st minute, 2nd hour 1 5 and 4th hour VAS levels in Group I was found to be statistically significant ($p < 0.006$). The difference between the post-op 1st minute and 4th hour VAS levels of Group II was found to be statistically significant ($p < 0.006$). In the post-op period, VAS levels of Group I at all times were higher than those of Group II and Group III, and this difference was statistically significant ($p < 0.006$). The difference between Group II and Group III in terms of VAS levels at all times in the postoperative period was not statistically significant ($p > 0.006$)(Figure 1).

Analgesic Requirement During Perioperative and Postoperative Period:

In the perioperative period, 4 patients in Group I, 2 patients in Group II and 3 patients in Group III needed analgesic. It was observed that the difference between the groups in terms of the number of patients who needed analgesic and the total amount of analgesic consumed during this period was not statistically significant ($p > 0.05$).

Postoperative first analgesic intake time was recorded as 240.0 ± 60.8 minutes in Group I, 378.1 ± 125.3 minutes in Group II and 486.7 ± 147.6 minutes in Group III. This period is shorter in Group I compared

to Group II and Group III, and this difference was found to be

statistically significant (p <0.001). The difference between Group II and Group III is not statistically significant (p> 0.001) (Figure 2).

The analgesic requirement during the postoperative period was 19 patients in Group I, 16 patients in Group II and 9 patients in Group III. The number of patients who needed analgesic in the postoperative period was less in Group III than the other two groups, and this difference was statistically significant (p <0.001).

The total analgesic consumption in the postoperative period is 1.7 ± 0.41 g in Group I, 0.7 ± 0.48 g in Group II and 0.3 ± 0.39 g in Group III. Total analgesic consumption is less in Group III compared to Group I and Group II, and this difference was statistically significant (p <0.001) (Table 4). Total analgesic consumption of Group II is less than Group I and this difference was found to be statistically significant (p <0.001).

The number of tablets used in Group III was statistically significantly lower than Group I and Group II. The number of tablets used in Group II was found to be less than Group I, and this difference is statistically significant (p <0.001).

Tourniquet Pain:
Tourniquet VAS levels according to time which was observed between the groups has no statistically significant difference (p <0.0125).

Sedation Scores:
No statistically significant difference was found between sedation scores according to time and groups (p> 0.006).

Anesthesia Quality:
Per-op 20 minute anesthesia quality was found to be lower in Group I compared to Group II and Group III, and this difference was considered statistically significant (p <0.001). In Group I, the anesthesia quality at the per-op 5th minute was higher than the anesthesia quality at the 15th and 20th minutes, and this difference was statistically significant (p <0.002) (Table 3).

DISCUSSION

Because IVRA can be applied easily compared to other peripheral nerve blocks, it is reliable, it is possible to keep blood loss at a minimal level during surgery, its cost compared to general anesthesia, its low postoperative complications, its rapid recovery and its easy application to the upper extremity, It is a preferred method in surgery (1, 5). However, in the event of intraoperative leaks and early opening of the tourniquet, monitoring the systemic toxic effects of local anesthetics, tourniquet pain, failure to provide the post-operative analgesia requirement may be among the reasons that limit the use of this technique (5).

In recent years, alpha-2 agonists (clonidine, dexmedetomidine), opioids (morphine, meperidine, fentanyl, sufentanil, tramadol), muscle relaxants, NSAIDs are (ketorolac, tenoxicam), dexamethasone, magnesium sulphate, neostigmine, nitroglycerin were used to increase the quality of anethsia (8-11).

Acute inflammation caused by tissue damage plays an important role in the onset of surgical pain and could theoretically be useful in the management of acute surgical pain as a result of the potent anti-inflammatory effect of dexamethasone (12). NSAID-induced analgesia is due to peripheral suppression of the cyclooxygenase enzyme, possibly due to reduced activation of the arachidonic acid cascade with

additional mechanisms. The local accumulation of Pg E and I2 is the result of surgical trauma and directs the sensitivity of the nociceptors of the A and C fibers. Inhibition of prostaglandin synthesis at the injury center reduces sensitization and leads to a reduction in postoperative pain. Pg E is produced by cyclooxygenase and dexketoprofen provides inhibition of this enzyme (13). Dexketoprofen is an NSAID drug from the arylpropionic acid group, which is the racemic S (+) - enantiomer of ketoprofen. Dexketoprofen trometamol acts by inhibiting the sensitization of pain receptors triggered by locally released prostaglandins. On the other hand, it reduces the central sensitization effect by inhibiting Cyclooxygenase (COX) activity, thus blocking the transfer of painful stimuli to the upper nerve centers (14).

In our study, in the IVRA method applied for hand and wrist surgical interventions, anesthesia quality of 3 mg / kg 0.5% lidocaine and dexamethasone and dexketoprofen added to it, the formation and recovery times of sensory and motor block, tourniquet pain, the time of first analgesic administration and total analgesic consumption We compared the effects on the amount of postoperative analgesic consumption, intraoperative and postoperative sedation.

Hoffmann et al. (15) They added saline, bupivacaine, clonidine, sufentanil and tenoxicam to prilocaine in their IVRA study conducted on 75 patients. They found that the time to onset of sensory block in the group containing sufentanil was statistically significantly shorter than in the saline group. There was no statistically significant difference between the sensory block rotation times of the groups. In their study conducted on 56 volunteers, Kleinschmidt et al. (10). 56 found no difference in the time of onset of sensory block and reversal between the groups when they gave prilocaine to the first group, prilocaine and clonidine to the second group, and prilocaine to the third group while using the prilocaine tourniquet on IVRA.

A study of Memiş et al. (16) found that the onset time of the sensory block was significantly less in the group with dexmedetomidine in the study performed by adding dexmedetomidine to lidocaine. A study of Armstrong et al. (17) added fentanyl to prilocaine in their study by adding sodium bicarbonate to prilocaine and found no significant difference in the time of occurrence and recovery of sensory blockade (17).

In the IVRA study conducted by Bigat et al. (9), on 75 patients, 3 mg / kg lidocaine in the first group, 3 mg / kg lidocaine and 8 mg dexamethasone in the second group, and 3 mg / kg lidocaine and systemic 8 mg dexamethasone gave intravenously. The recovery time of the sensory block after tourniquet was removed was longer in the dexamethasone group than the others. A study of Jankovic et al.(13) added ketorolac along with ketorolac and dexamethasone to lidocaine in their study of 45 patients and found the groups to be similar in terms of sensory block onset time and sensory block recovery time after the tourniquet was released. In our study, the onset of sensory block was an average of 3 (2-4) minutes in Group I, 3 (2-5) minutes in Group II and 2.5 (2-5) minutes in Group III. The sensory block recovery time was 9 (6-11) minutes in Group I, 10 (7-11) minutes in Group II, and 9 (6-11) minutes in Group III. In our study, no difference was observed between the groups in terms of the onset of sensory block and its return.

In studies investigating the effects of adjuvant agents in IVRA, it was found that the addition of magnesium sulfate, nitroglycerine, cisatracurium or tramadol to lidocaine shortened the onset of motor block and significantly prolonged the motor block recovery time (9, 11, 18¬20).

In the study in which dexamethasone and ketorolac added to lidocaine, no difference was found

between the onset and end times of motor block (13). In the study in which they mixed dexamethasone with IVRA solution or applied systemically, the motor block onset time was found to be similar between the groups, while the motor block return time was found to be significantly higher in the group with dexamethasone (12). In our study, the motor block onset time was 7 (5-8) minutes in Group I, 7 (5-10) minutes in Group II, and 6 (5-8) minutes in Group III. Block onset time in group III was statistically significantly shorter than the other two groups. We think that the shorter duration in group III may be related to dexketoprofen. We could not find an IVRA study conducted with dexketoprofen in the literatüre. However, A study of Şen et al. (21), in which they added another NSAID, lornoxicam, to lidocaine, the motor block onset time was found to be shorter and the return time to be longer.

One of the disadvantages of IVRA application is tourniquet pain that can occur 30-60 minutes after the toumiquet is inflated. A study of Esmaoğlu et al. (19) found that VAS values at 0, 15, 30 and 60 minutes were significantly lower in the group to which dexmedetomidine was added to lidocaine. The study of Şen et al. (21) study was found that the pain of tourniquet was decreased in the study by adding lornoxicam to lidocaine.

The study of Bigat et al. (12) study was found that tourniquet pain control was better in the group in which dexamethasone was added to lidocaine. The study of Jankovic et al. (13) study in which dexamethasone and ketorolac were added to lidocaine, the results were similar. In our study, in which we planned to administer 1 pg / kg fentanyl to patients with tourniquet pain in the intraoperative period, fentanyl was administered only to one patient in Group III. Other than that, no patient required analgesic due to tourniquet pain. This may be because the operation times in our study were relatively short. Studies with long tourniquet durations can be planned to determine the intraoperative analgesic effect of dexamethasone and dexketoprofen more reliably.

A study of Reuben et al. (22) study in which ketorolac added to lidocaine, intraoperative VAS values were found to be significantly lower in the ketorolac group. The study of Jankovic et al. (13) study in which ketorolac and dexamethasone added to lidocaine, intraoperative VAS levels were found to be lower at all times. In our study, no statistically significant difference was found between the groups in terms of VAS levels in the intraoperative period. In the postoperative period, Group I VAS levels were higher than the other two groups at all times, and the difference was statistically significant. At all times, there was no difference between Group II and Group III in terms of VAS. (Table 3)

In our study, fentanyl requirement in the intraoperative period was 4 patients in Group I, 2 patients in Group II and 3 patients in Group III. There was no difference between the groups in terms of average fentanyl consumption.

As a result of these results, the quality of anesthesia and analgesia in the intraoperative period was evaluated as sufficient. The study of Bigat et al. (12) study has also been shown in the studies that dexamethasone was added to provide better postoperative analgesia. The study of Jankovic et al. (13) study was found that better postoperative analgesia was provided with tenoxicam and dexamethasone. In our study, we think that the low VAS values in Group II and Group III in the postoperative period are caused by dexamethasone and dexketoprofen added to lidocaine.

Although IVRA is an easy-to-apply, reliable and low-cost anesthesia technique, one of its major disadvantages is the rapid disappearance of analgesia following the tourniquet opening and the need for postoperative analgesic use. The effects of adjuvant drugs used in the studies on analgesia were also investigated. The study of Reuben et al. (22) study of IVRA, it was seen that the use of ketorolac both

facilitated the control of tourniquet pain and decreased postoperative pain.

The study of Şen et al. (23) study by adding nitroglycerine to lidocaine, the first analgesic requirement was found to be 225 ± 74 minutes, and it was found that analgesic activity continued longer than the control group. In addition, in this study, it was found that the pain score was lower for the first 4 hours postoperatively compared to the control group.

A study of Turan et al. (11) study of lidokaine magnesium sulfate, The study of Şen et al. (21) study of lornoxicam, The study of Esmaoğlu et al. (20) study was shown that the first analgesic requirement time was long and postoperative VAS values were signifıcantly lower in the first hour in the groups in which the adjuvant agent was added.

Likewise, The study of Bigat et al.(12) of lidocaine dexamethasone, A study of Öztürk et al. (24) of lidocaine tenoxicam, A study of Tuncer et al. (25) was found that the duration of postoperative analgesia was prolonged and the pain intensity was less in the studies of prilocaine with meperidine.

A study of Memiş et al (16) in IVRA, where dexmedetomidine was added to 3 mg / kg lidocaine, the first analgesia requirement time was longer than the control group and VAS values were lower in the first hour after the tourniquet was opened.

The study of Esmaoğlu et al. (19) performed by adding dexmedetomidine to lidocaine, it was found that the quality of anesthesia increased and the analgesic requirement decreased.

In the study of Turan et al. (8), while the first analgesic requirement time was found longer in the neostigmine group compared to the control group, no statistical difference was found in terms of VAS values.

In the study of McCartney et al., (26) No significant difference was found between the neostigmine group and the control group in terms of the time of first analgesic requirement and VAS values.

In our study, the postoperative analgesic requirement was 19 (100%) in Group I, 16 (84%) in Group II and 9 (50%) in Group III. The difference between Group I and Group II was not statistically significant, but the difference of Group III with other groups was found to be statistically significant. The first analgesic intake was 240 ± 60.8 minutes in Group I, 378 ± 125.3 minutes in Group II and 486 ± 147.6 minutes in Group III. Total analgesic consumption was also found to be 1.7 ± 0.41 g in Group I, 0.7 ± 0.48 g in Group II and 0.3 ± 0.39 g in Group III. In our study, no side effects related to the drugs used were observed in any patient.

In conclusion, adding dexamethasone and dexketoprofen to lidocaine prolongs the time of first analgesic intake and decreases the total amount of analgesic use in the postoperative period. However, further studies may be needed to investigate the local action mechanism of dexketoprofen.

CONCLUSION

In our study, we observed that 8 mg dexamethasone and 50 mg dexketoprofen added to lidocaine in IVRA prolonged the postoperative first analgesic intake time and analgesia time without any side effects and reduced the total analgesic consumption amount. In conclusion, by adding dexamethasone and dexketoprofen to lidocaine, better quality anesthesia, postoperative analgesia can be provided and postoperative analgesic consumption can be reduced.

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Table 1. Demographic variables

Variables	**Group I (n=19)**	**Group II (n=19)**	**Group II (n=18)**	***p***
Age (years)	49,9 ± 14,0	49,0 ± 8,5	45,7 ± 12,5	0,526
Gender				0,948
Man (n)	8 (%42,1)	9 (%47,4)	8 (%44,4)	
Woman (n)	11 (%57,9)	10 (%52,6)	10 (%55,6)	
Weight (kg)	71,7 **± 13,9**	75,5 **± 13,4**	71,5 **± 15,6**	0,623
ASA				0,613
ASA I (n)	8 (%42,1)	9 (%47,4)	10 (%55,6)	
ASA II (n)	10 (%52,6)	10 (%52,6)	8 (%44,4)	
ASA III (n)	1 (%5,3)	0 (%0)	0 (%0)	

Table 2 Distribution of sensory and motor block ınitiation and end times by groups

Variables	**Group I (n=19)**	**Group II (n=19)**	**Group II (n=18)**	***p***
SB Initiation Time (min.)	3 (2-4)	3 (2-5)	2,5 (2-5	0,400
SB Initiation Time (min.)	9 (6-11)	10 (7-11)	9 (6-11)	0,385
MB End Time (min.)	7 (5-8)[a]	7 (5-10)[b]	6 (5-8)[a,b]	0,002
MB End Time (min.)	10 (7-13)	10 (9-13)	10 (7-13)	0,424

SB: Sensorial Block, MB: Motor Block

a The difference between Group I and Group III is statistically significant (p=0.006)
b The difference between Group II and Group III is statistically significant (p<0.006)

Table 3. Anesthesia quality scores by time and groups

Follow up Time	Group I	Group Iı	Group III	p^a
Per-op 5 min.	4,0	4,0	3,9	0,348
Per-op 10 min.	3,9	3,8	3,8	0,847
Per-op 15 min.	3,4	3,8	3,8	0,014
Per-op 20 min.	3,3	3,8	3,8	<0,001

a Results for p <0.0125 were considered statistically significant according to the Bonferroni Correction.

b The difference between Per-op 5 min and Per-op 15 min is statistically significant (p <0.002).

c Per-op 5.dk ile Per-op 20.dk arasındaki fark istatistiksel olarak anlamlı (p<0,001).

d Grup I ile Grup II arasındaki fark istatistiksel olarak anlamlı (p<0,001).

e Grup I ile Grup III arasındaki fark istatistiksel olarak anlamlı (p<0,001).