Effect of Alprazolam as a Preoperative Adjuvant Analgesic on Postoperative Pain in Laparoscopic Donor Nephrectomy Patients

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ABSTRACT

Objective. The aim of this study was to evaluate the effectiveness of alprazolam, administered at different doses, for the control of adjuvant analgesia in laparoscopic donor nephrectomy patients preoperatively in the Akdeniz University Organ Transplantation Center, using various pain scales.

Materials and Methods. Only patients with a body mass index $\leq$28 kg/m^2, aged between 18 and 65 years old, and with an American Society of Anesthesiologists score of 1 to 2 were included in the study. The patients were studied in 3 groups, which were given 0.5 mg alprazolam (group 1), 1 mg alprazolam (group 2), or no alprazolam (group 3) in the preoperative period. Collected data were evaluated for preoperative, intraoperative, and postoperative periods.

Results. There were 75 patients (31 men, 44 women). Mean age was 43.1 years. Twenty-five patients were evaluated in all 3 groups. Mean operation time was 137.8 minutes. There was no statistical difference among the groups in the duration of administered alprazolam before the operation, on the Ramsey sedation score, verbal pain score, or numeric pain score, and duration of administered first analgesic in the postoperative period. Additional dose of analgesics were administered in 7, 7, and 11 of the patients in group 1, group 2, and group 3, respectively. We found a significant difference between groups 1 and 2 in blood pressure ($P = .017$ and $P = .014$). We found a significant difference in group 1 in heart rate ($P = .002$).

Conclusion. More effective analgesia protocols need to be identified for pain control in patients of laparoscopic donor nephrectomy. It is thought that the effectiveness of pain control may increase the number of donors and progress in the treatment of patients with renal failure.

LAPAROSCOPIC donor nephrectomy (LDN) was first performed in 1995 on a human [1]. When compared with cadaveric donor kidney transplants, living donor kidney transplants have better results because of shorter warm and cold ischemia durations [2–4]. Clinical and surgical advantages of LDN compared with open nephrectomy include better cosmetic results with a smaller incision, lower incisional hernia rate, adhesion rate, postoperative pain, shorter hospital stay, and faster return to work [2]. Disadvantages of LDN include longer duration of warm ischemia, operation time, and learning curve and higher risk of life-threatening bleeding events, liver and spleen laceration, pancreatitis, bowel injury, diaphragmatic injury, pneumonia, and pneumothorax [5,6]. Chin et al [7] reported the complication rate of 500 patients during and after the operation was 5.8% and

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8.8%, respectively. In another study, complication rates during and after the operation were as 6.8% and 17.1%, respectively [5].

Alprazolam is an 8-chloro-1-methyl-6-phenyl-4H-s-triazolo(4,3-a) [1,4] benzodiazepine. After single-dose oral administration, alprazolam exhibits a serum half-life of 12 to 15 hours (D.M. Wellngford et al, unpublished data, 1981) [8]. After a single oral dose of 0.5 to 3 mg, the peak serum concentration is reached after 0.7 to 2.1 hours and peak serum levels reach 7.35 to 39.2 ng/mL. Independent of dose, 80% of the alprazolam is absorbed after oral administration [7]. Eighty percent of alprazolam binds to plasma proteins, the majority of which is albumin (68%) (D.M. Wellngford et al, unpublished data, 1981) [9,10]. Alprazolam is used in the treatment of generalized anxiety disorders, short-term anxiety and anxiety-related depression, and panic disorders associated with or without agoraphobia [11]. Results of double-blinded placebo-controlled trials showed that women with premenstrual dystrophic disorder improved with alprazolam in the luteal phase, but no symptomatic improvement was observed in the postmenstrual phase [12–14]. Alprazolam in combination with ibuprofen has been also shown to be effective in primary fibrositis and fibromyalgia syndrome [15]. The most common side effects of alprazolam are drowsiness, dizziness, fatigue, dysarthria, headache, memory impairment, and depression [16].

Lower pain experience in any living donor surgery is essential in order to increase donation rates. This study quantitatively analyzed (via various pain scales) the adjuvant analgesic efficiency of different doses of preoperative alprazolam in LDN patients at Akdeniz University Organ Transplantation Center. Thus, the objective of the study was twofold. The first objective was to provide a precise and systematic pain assessment. The second objective was to promote comfort in LDN procedures.

MATERIALS AND METHODS

From January 2017 to November 2017, we studied 173 LDN cases who were 18 to 65 years old and had an American Society of Anesthesiologists 1 or 2 score, no allergies, and a body mass index $\leq$28 kg/m^2 at the Akdeniz University Organ Transplant Center. Data of the patients were obtained retrospectively from hospital records. From the data, the patients age, sex, harvested kidney side (right vs left), preoperative vital signs (body temperature, heart rate, and blood pressure), intraoperative and postoperative complication status, operation time, vital signs before administration of first analgesic, verbal pain score (VPS), numeric pain score (NPS), Ramsey sedation score (RSS), time of administration of first analgesic after the surgery, and additional dose of analgesic status were collected and analyzed for the preoperative, intraoperative, and postoperative periods. Ninety-six patients were excluded because of insufficient data. Two of 77 patients were excluded because of intraoperative and postoperative complications, and the remaining 75 patients were included in the study. The patients were evaluated in 3 groups: preoperative 0.5 mg alprazolam (group 1), 1 mg alprazolam (group 2), and no alprazolam (group 3). We had 25 patients in all 3 groups.

In our center, LDN patients' pain status were routinely evaluated with VPS, NPS, and RSS; according to this evaluation, analgesics were administered. The patients at RSS $\leq$3 were considered to have sufficient consciousness and evaluated with VPS and NPS. We administered analgesic to patients with score of VPS $\geq$2 and NPS $\geq$3. Tramadol 100 mg and paracetamol 500 mg were infused intravenously, twice a day. If the patient needed an analgesic before the second dose, we counted it as an additional dose analgesic. In our center, we evaluated the donor and recipients in a preoperative transplantation council and decided from which side the kidney will be taken. Akdeniz University Faculty of Medicine Ethics Committee approval was obtained for this study.

Statistical Analysis

IBM-SPSS version 20.0 for Mac OS (IBM, Armonk, NY, United States) was used for statistical analysis of the collected data. To define the sample, continuous variables were specified as mean $\pm$ standard deviation, median (minimum-maximum), and categorical variables as a number and percentage. The normal distribution of continuous variables was evaluated by the Shapiro-Wilk test. The difference of the percentages of categorical variables was analyzed by the Pearson χ^2 test. Paired samples t test was used for the analysis of the difference between 2 groups in the cases where the parametric test assumptions were used and the Wilcoxon signed-rank test was used for the nonparametric test when the parametric test assumptions were not met. In the cases where parametric test assumptions were used, the difference between 2 independent group averages was analyzed by Student t test, and when the parametric test assumptions were not met, the nonparametric alternative to this test was examined by Mann-Whitney U test. In the cases where the parametric test assumptions were met, the difference between 2 independent group averages was analyzed with one-way analysis of variance, and when the parametric test assumptions were not met, the nonparametric alternative of this test was examined with Kruskal Wallis test. Pearson correlation analysis was used to determine the relationship between 2 groups. An error margin of $\alpha = 0.05$ (or 95% significance level) were used to determine the differences in the analyses.

RESULTS

In the preoperative period, we collected the patients' sex, age, kidney side to be harvested, and the vital signs. In intraoperative period, we collected operation time and the time of administered alprazolam before surgery. In postoperative period, we collected vital signs before administering the first analgesics, time of first administered analgesic after the surgery, additional dose of analgesics administered, RSS, VPS, and NPS. We found no significant difference for all parameters. When we checked the data of additional dose of analgesic, we noticed that the opioid type of analgesic consumption was lower, and the time of administration of an additional dose of analgesic were longer in group 2 patients. These findings are shown in Tables 1–3.

We found a significant difference for systolic blood pressure change in group 1 patients and for systolic and diastolic blood pressure change in group 2 patients and found no significant differences for systolic and diastolic blood pressure change in group 3 patients when we

Table 1. Preoperative Period

	All Patients	Group 1	Group 2	Group 3
Age, mean ± SD, y	43.1 ± 11.9	42.56 ± 11.26	41.16 ± 12.88	48.84 ± 11.51
Sex, No. (%)				
Male	31 (41.3)	10 (40)	12 (52)	8 (32)
Female	44 (58.6)	15 (60)	13 (48)	17 (68)
Harvested kidney, No. (%)				
Right	25 (33.3)	10 (40)	5 (20)	10 (40)
Left	50 (66.6)	15 (60)	20 (80)	15 (60)
Body temperature, mean ± SD, °C	36.3 ± 0.19	36.24 ± 0.44	36.24 ± 0.44	36.08 ± 0.28
Systolic blood pressure, mean ± SD, mm Hg	125.7 ± 19.5	126.64 ± 17.23	123.68 ± 20.85	126.96 ± 21.09
Diastolic blood pressure, mean ± SD, mm Hg	72.8 ± 10	71.96 ± 7.31	71.28 ± 11.09	75.32 ± 11.25
Heart rate, mean ± SD, beats/min	74.2 ± 13.5	74.52 ± 12.25	71.52 ± 12.86	76.64 ± 15.46

Age, $P = .367$; sex, $P = .353$; body temperature, $P = .25$; heart rate, $P = .41$; systolic blood pressure, $P = .81$; diastolic blood pressure, $P = .32$.
Abbreviation: SD, standard deviation.

compared the preoperative and postoperative period. The average change in systolic blood pressure in groups 1, 2, and 3 were as follows; −11.52 mm Hg ($P = .007$), −13.56 mm Hg ($P = .017$), and −5.88 mm Hg ($P = .325$), respectively. The average change in diastolic blood pressure in group 1, 2, and 3 were as follows: −4.92 mm Hg ($P = .131$), −8.68 mm Hg ($P = .014$), and −1.4 mm Hg ($P = .674$), respectively. We found no significant difference for the heart rate in group 1 and 3 patients but found significant difference in group 2 patients when we compared the preoperative and postoperative period. The average change in heart rate in groups 1, 2, and 3 were as follows: −13.6 beats/min ($P = .002$), −3.36 beats/min ($P = .313$) and −1.88 beats/min ($P = .654$), respectively.

We also compared the pain between men and women. In our study, 13 of 25 patients were women who were administered an additional dose analgesic. For 16 patients, tramadol was chosen as additional dose analgesic; 10 of them were women and 6 of them were men. In group 1, we found that VPS was 4.7 ± 0.67 and NPS was 7.3 ± 1.16 in men and VPS was 4.87 ± 0.83 and NPS was 8.07 ± 1.39 in women. First-time analgesic administration average time were found as 67.8 ± 22.4 minutes in men and 60.4 ± 20.37 minutes in women. We found no statistical difference for sex in group 1 VPS ($P = .655$), NPS ($P = .155$), and first time analgesic administration average time after surgery ($P = .54$). In group 2, we found VPS was 4.57 ± 0.78 and NPS was 7.56 ± 1.45 in men and VPS was 4.33 ± 0.98 and NPS was 7.5 ± 1.24 in women. First-time analgesic administration average time was found as 77.15 ± 37.65 minutes in men and 118 ± 208.69 minutes in women. We found no statistical difference for sex in group 2 VPS ($P = .507$), NPS ($P = .843$), and first-time analgesic administration average time after surgery ($P = .90$). In group 3, we found VPS was 4.63 ± 1.06 and NPS was 7.38 ± 2.26 in men and VPS was 4.88 ± 1.05 and NPS was 8.06 ± 1.43 in women. First-time analgesic administration average time were found as 74 ± 30.56 minutes in men and 79.06 ± 44.84 minutes in women. We found no statistical difference for sex in group 3 VPS ($P = .464$), NPS ($P = .55$), and first-time analgesic administration average time after surgery ($P = .705$).

DISCUSSION

Based on the results of a study evaluating a total of 45 patients treated with placebo, ibuprofen, and ibuprofen + alprazolam in which pain control after orthodontic treatment was evaluated 6 hours after a procedure, VPS was found to be better in patients receiving ibuprofen + alprazolam when compared with others [17]. According to the results of a study of 76 patients who underwent total knee arthroplasty because of osteoarthritis, patients who were administered alprazolam combined with diclofenac had better VPS when compared with patients administered only diclofenac [18]. These arthroplasty patients were evaluated with the Hamilton anxiety rating scale and Beck depression inventory; as a result, administering a benzodiazepine derivate medicine to those patients in the preoperative period was recommended [18]. In our study, differently from those studies, we did not evaluate patients with anxiety and depression scores because our population were evaluated by a psychiatry specialist at the donation period; also, we evaluated pain with VPS and NPS together and found no difference among the groups. We also evaluated the patients with RSS. As we expected, we found no statistical difference between groups for RSS ($P = .747$) because we evaluated RSS only for sufficient consciousness after general anesthesia.

Table 2. Intraoperative Period

	All Patients	Group 1	Group 2	Group 3
Operation time, mean ± SD, min	137.8 ± 43	136.6 ± 46.2	144.96 ± 41.64	132.04 ± 41.69
Time of administered alprazolam before surgery, mean ± SD, min		259.8 ± 91.5	241.2 ± 82.7	None

Operation time, $P = .56$; time of administered alprazolam before surgery, $P = .45$.
Abbreviation: SD, standard deviation.

Table 3. Postoperative Period

	All Patients	Group 1	Group 2	Group 3
Body temperature, mean ± SD, °C	35.9 ± 1.2	36 ± 0.3	36 ± 0.3	35.6 ± 2
Systolic blood pressure, mean ± SD, mm Hg	136 ± 20	138.1 ± 16.1	137.2 ± 18.9	132.8 ± 24.5
Diastolic blood pressure, mean ± SD, mm Hg	77.8 ± 14.4	76.8 ± 14.7	79.9 ± 11.6	76.7 ± 16.9
Heart rate, mean ± SD, beats/min	80.5 ± 14	77.8 ± 13.5	85.1 ± 15.3	78.5 ± 12.4
Time of first administered analgesics, mean ± SD, min	79.1 ± 87.7	63.3 ± 21	96.7 ± 145.2	77.4 ± 40.2
Additional dose of analgesic, No.				
Tramadol	16	5	3	8
Paracetamol	9	2	4	3
Time of additional dose of analgesic, mean ± SD, min	471.6 ± 102.9	482.8 ± 77.1	467.1 ± 122.3	460.9 ± 111.4
RSS ± SD	Null	2.1 ± 1	2.2 ± 0.9	2 ± 0.7
VPS ± SD		4.8 ± 0.7	4.4 ± 0.8	4.8 ± 1
NPS ± SD		7.7 ± 1.3	7.4 ± 1.3	7.8 ± 1.7

Body temperature, $P = .51$; heart rate, $P = .13$; systolic blood pressure, $P = .61$; diastolic blood pressure, $P = .67$; time of first administered analgesic, $P = .40$; additional dose of analgesic, $P = .389$; time of additional dose of analgesic, $P = .82$; RSS, $P = .747$; VPS, $P = .269$; NPS, $P = .664$.

Abbreviations: NPS, numeric pain score; RSS, Ramsey sedation score; SD, standard deviation; VPS, visual pain score.

Fernandez et al [19] has reported similar result to our study. Patients with cancer with neuropathic, somatic, and mixed pain were evaluated after administering 1.5 to 4 mg/day alprazolam. Twelve of the 19 patients with neuropathic pain had relief in pain completely, 5 of them had relief in pain particularly; 5 of 10 patients with mixed pain had relief in pain completely; none of patients with somatic pain had relief in pain. Joseph et al [20] has compared the effect of 600 mg gabapentin, 0.5 mg alprazolam, and placebo on postoperative pain and anxiety in abdominal hysterectomy patients and reported that the effect of 0.5 mg alprazolam on anxiety was superior from others; however, 0.5 mg alprazolam and 600 mg gabapentin didn't alter the dose of narcotic analgesic consumption when compared with placebo. Also, similarly to our study, they didn't administer any nonsteroidal anti-inflammatory agents to the patients and didn't find an effect on postoperative pain. Differently from our study, the patients were administered analgesic with a patient-controlled analgesic pump. Instead of a patient-controlled analgesic pump, we evaluated the patients with VPS and NPS for analgesic need as described before. Administration of alprazolam average time before surgery was 270.06 ± 106.57 minutes and 233.71 ± 15.66 minutes in group 1 for patients with no additional dose of analgesic administered and patients with an additional dose of analgesic administered, respectively. Administration of alprazolam average time before surgery was 252.22 ± 80.75 minutes and 213 ± 87.45 minutes in group 2 for patients with no additional dose of analgesic administered and patients with an additional dose of analgesic administered, respectively. We found no significant difference in statistical analysis in groups 1 and 2 at this parameter ($P = .384$ and $P = .297$ in group 1 and 2, respectively).

Miaskovski et al [21] has reported that women consumed less opioid analgesics than men in the postoperative period. In our study, we found no statistically significant difference between men and women for opioid consumption and for their pain scores. In a placebo-controlled study, the effects of 1.5 mg alprazolam were examined on blood pressure and blood cortisol level and reported as lower in the alprazolam-administered group [22]. Similarly to this study, in our study, we found a significant difference for systolic blood pressure in group 1 patients and for systolic and diastolic blood pressure in group 2 patients and found no significant differences for systolic and diastolic blood pressure in group 3 patients. The average change in systolic blood pressure in group 1, 2, and 3 were found as −11.52 mm Hg ($P = .007$), −13.56 mm Hg ($P = .017$) and −5.88 mm Hg ($P = .325$), respectively. The average change in diastolic blood pressure in groups 1, 2, and 3 were found as −4.92 mm Hg ($P = .131$), −8.68 mm Hg ($P = .014$), and −1.4 mm Hg ($P = .674$), respectively. In another study, effects of captopril and alprazolam on blood pressure were evaluated in patients who were admitted to emergency service with high blood pressure, and they reported that the effects of both agents were similar in lowering blood pressure [23]. In this study, differently from ours, 96.2% of patients had a high anxiety score; similarly to our study, they found a significant difference in lowering blood pressure and anxiety score with 0.5 mg alprazolam.

In a controlled study, the effect of 0.5 mg alprazolam administered 30 to 45 minutes before transaction, heart rate variability, and image quality of 64-slice multi-detector computed tomography coronary angiography were evaluated. They reported that heart rate variability was lesser and the image quality was better in patients who were administered 0.5 mg alprazolam during the transaction [24]. In our study, we did not evaluate this parameter, but we evaluated preoperative and postoperative heart rate difference. In group 2 patients, we found a significant change in preoperative and postoperative heart rate with a value of −13.6 beats/min and $P = .002$. In group 1 and 3, we found no significant changes with this parameter (change value −3.36 and −1.88; $P = .313$ and $P = .654$, respectively).

CONCLUSION

In this study, we found that alprazolam was not effective for postoperative pain; in conclusion it is suggested that different

and more effective analgesia protocols should be used for pain control in patients of laparoscopic donor nephrectomy, or different analgesics should be applied in the preoperative period for pain control. We have found that our work has 2 deficiencies. There were 75 cases in our study that met the appropriate criteria. We found that our standard deviation rates were higher in statistical analysis, which suggests that the number of cases taken to work is not sufficient. It was also determined that the additional dose of analgesia was decided by the clinician or nurse, regardless of VPS and NPS. There is no published study of postoperative pain control in LDN cases. In this respect, our work is an original work. In addition, there are not enough studies to measure the effect of preoperative alprazolam in pain control in the postoperative period. Ratner et al [25] reported that 40% of living kidney donors would not donate if there was no laparoscopic surgery technique and would not accept open surgery. It is also believed that a more efficient provision of pain control may result in an increase in the number of living kidney donors and may progress the treatment of patients with end-stage renal failure. For this reason, we think that new studies should be done about this subject.

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