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Research Article
Effects of Dexmedetomidine and Ketamine on Oxidative Stress Markers in Patients Undergoing Lower Extremity Surgery: A Randomized, Double-Blind Study

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Abstract

Background and Objective: Surgical procedures trigger neuroendocrine, immunological, inflammatory, metabolic and endocrine responses in the body. To minimize the surgical stress response, various methods are recommended, such as the use of combined anesthetic techniques, intrathecal drug combinations and perioperative drug administration. This study compared the effects of intravenously administered dexmedetomidine and ketamine on serum malondialdehyde (MDA), Heme Oxygenase-1 (HO-1) and C-Reactive Protein (CRP) levels in patients undergoing lower limb surgery with combined spinal epidural anesthesia (CSEA). **Materials and Methods:** Three groups were formed (n = 30, for each group): Group 1 patients were administered isotonic 10 cc/hr IV infusion, Group 2 patients were administered dexmedetomidine as a 0.1 μg/kg IV bolus followed by a 0.2 μg/kg/hour IV infusion and Group 3 patients were given ketamine as a 0.2 mg/kg IV bolus followed by a 0.1 mg/kg/hr IV infusion throughout the surgery. All patients received CSEA in a seated position. Blood samples for malondialdehyde (MDA) and Heme Oxygenase-1 (HO-1) analysis were taken at preoperative (T0), 2nd hr of surgery (T1) and 24th hr postoperatively (T2). **Results:** The lower serum MDA and higher serum HO-1 levels at the 2nd hr of surgery and the 24th hr after surgery were found in Group 2 and 3 compared to Group 1. Groups 2 and 3 had similar serum MDA and HO-1 levels at the 2nd hr of surgery and the 24th hr after surgery. **Conclusion:** The effects of dexmedetomidine and ketamine administered via IV infusion after the loading dose on serum MDA and HO-1 levels were similar in patients undergoing lower extremity surgery under CSEA. In appropriate cases, both agents can be used as sedatives and anxiolytics to reduce neuroendocrine stress responses associated with surgery and anesthesia.

Key words: Surgical stress, ketamine, dexmedetomidine, malondialdehyde, heme oxygenase-1, anesthesia

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Surgical procedures trigger a stress response in the body. This situation involves neuroendocrine, immunological, inflammatory, metabolic and endocrine responses[1]. Type of surgical procedure and the anesthetic agents may influence the stress response[2,3]. To minimize the surgical stress response, various methods are recommended, such as the use of combined anesthetic techniques, intrathecal drug combinations, perioperative drug administration, high-dose opioids and beta-blocker usage[4-8].

Heme oxygenase is the rate-limiting enzyme in the reaction where heme is catabolized to biliverdin by releasing carbon monoxide (CO) and free iron. The CO is a direct indicator of endogenous heme catabolism and studies mention its vasodilatory, anti-inflammatory, anti-apoptotic and anti-proliferative properties[9,10]. Malondialdehyde, a product of lipid peroxidation, is used as an indicator of oxidative stress[11].

Dexmedetomidine, a selective alpha-2 agonist drug, has sedative and antinociceptive effects and is used as an adjuvant in regional anesthetic techniques[12]. It was reported that using dexmedetomidine during the perioperative period reduces the requirements of opioids and anesthetic drugs with favorable neuroendocrine and hemodynamic responses[13]. Ketamine, another adjuvant used in anesthesia, has sympatholytic, analgesic and sedative effects. However, the use of low-dose ketamine is known to cause undesirable symptoms like delirium and agitation[14]. There are conflicting results in the literature concerning the occurrence of these symptoms. In a study by Bornemann-Cimenti *et al.*[15] conducted on patients undergoing elective major abdominal surgery low-dose S-ketamine led to the highest delirium scores compared to the minimal-dose S-ketamine and placebo. On the other hand, Subramaniam *et al.*[16] reported that very low-dose ketamine infusion had no central nervous system side effects and did not improve postoperative pain scores. In another study by Kator *et al.*[17], significant cardiovascular adverse effects were reported in patients treated with adjunctive low-dose ketamine for analgesia. In this case, authors hypothesized that dexmedetomidine would be effective in reducing postoperative pain compared to ketamine, with better surgical stress response and fewer central nervous system side effects. Therefore, this study compared the effects of intravenously (IV) administered dexmedetomidine and ketamine on postoperative oxidative stress markers including malondialdehyde (MDA), Heme Oxygenase-1 (HO-1) and C-Reactive Protein (CRP) levels in patients undergoing lower limb surgery using combined spinal epidural anesthesia (CSEA).

The secondary objective was to compare hematological and biochemical parameters, heart rate (HR), mean arterial pressure (MAP) and Visual Analog Scale (VAS) values during the postoperative period among groups.

MATERIALS AND METHODS

Study area: This prospective, double-blind, randomized controlled trial was conducted in the operating rooms of Ataturk University, Faculty of Medicine, Erzurum, Turkey between December, 2021 and May, 2023.

Ethical consideration: The study was initiated after obtaining approval from the Faculty of Medicine, Clinical Research Ethics Committee, Ataturk University (protocol number: B.30.2.ATA.0.01.00/23, date: 30.12.2021). The study was supported by the Scientific Research Projects Coordination Unit, Ataturk University (23.02.2022, Project Number: TTU-2022-10336, ID: 10336).

Study design: The study population is comprised of 90 consecutive patients ASA I-II, aged between 18-65 years, a Body Mass Index (BMI) $\leq$30 kg/m^2 undergoing elective lower limb surgery with CSEA technique[18]. Patients with increased intracranial and intraocular pressure, psychiatric and neuromuscular disorders and vascular and coronary diseases were excluded. Patients with coagulation disorders, allergy to study drugs, BMI above 30 kg/m^2, those requiring cement used in the surgical procedure, those to whom a tourniquet would be applied to the lower extremity, patients with multiple trauma and those who did not consent to participate in the study were also excluded.

Written informed consent was provided by all participants.

Evaluation of patients was conducted by a researcher blinded to group assignment one day before the surgery. During this consultation, patients who met the inclusion criteria were informed about the study and written consent was obtained from those who agreed to participate. Peripheral intravenous access was established using a 16/18-gauge cannula. No premedication was administered. Prior to the anesthesia procedure, all patient's ASA physical status, age, weight, height, BMI, baseline blood pressure values, heart rates and oxygen saturation levels were recorded. This study was planned as double-blind; the patient and the researcher evaluating and recording the patient's data were unaware of which group the patient belonged to. The randomization sequence was done using a computer-generated table of random numbers. An anesthetist opened the envelopes and the patients were divided into 3 groups with 30 patients

in each group: Group 1 patients were administered isotonic 10 cc/hr IV infusion, Group 2 patients were administered dexmedetomidine (Dexdomed®, Polifarma Pharmaceuticals, Turkey) as a 0.1 µg/kg IV bolus followed by a 0.2 µg/kg/hr IV infusion and Group 3 patients were given ketamine (Ketalar®, Pfizer, Turkey) as a 0.2 mg/kg IV bolus followed by a 0.1 mg/kg/hr IV infusion throughout the surgery. Another anesthetist, blinded to group allocation, recorded intraoperative and postoperative data. All surgeries were performed by the same surgical and anesthesia teams.

All patients received CSEA in a seated position. After skin sterilization and infiltration with 2% lidocaine (Aritmal®, Osel Pharmaceuticals, Turkey), an 18-gauge Tuohy needle (Braun, Melsungen, Germany) was advanced using the loss of resistance technique along the midline of the L3-4 or L4-5 intervertebral spaces. After detecting negative pressure, a 27-gauge pencil-point spinal needle was inserted intrathecally using the needle-through-needle technique. Following the observation of free cerebrospinal fluid flow, 1.8 mL of 0.5% isobaric bupivacaine (9 mg) (Buvasin®, Vem Pharmaceuticals, Turkey) and 15 µg of fentanyl (Fentanyl Citrate®, Hospira, USA) were administered for 30 sec. Subsequently, the spinal needle was removed, and an epidural catheter was placed and secured after advancing 3-5 cm into the epidural space and confirming negative pressure. At the end of the anesthesia procedure, the patients were placed in a supine position for surgery. The study drugs necessary according to the assigned study group were initiated and infusions continued throughout the surgical procedure.

The sensory block level was assessed using the pinprick test and when the sensory block reached the upper level of the T12-L1 dermatome, the surgery was initiated. Patients were excluded from the study if no sensory block had occurred within the first 20 min following spinal injection. In cases where intrathecal access was not achieved in three unsuccessful attempts, a general anesthesia protocol was planned and these patients were excluded from the study.

The motor block level was assessed using the modified Bromage scale (0 = the patient can move hip, knee, ankle and toes; 1 = the patient can flex the knee and extend the foot, unable to flex the hip; 2 = the patient can flex the foot, unable to flex the knee and hip; 3 = total motor block). Sensory block level and Bromage scores were assessed and recorded at 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105 and 120 min following intrathecal injection.

During the surgery, patients were provided with oxygen through a nasal cannula. In the event of hypotension (defined as a 20% decrease in systolic blood pressure compared to preoperative values), intravenous ephedrine (6 mg) (Ephedrine Hydrochloride®, Osel Pharmaceuticals, Turkey) was administered as a vasopressor. If bradycardia occurred (heart rate <45 beats per min), intravenous atropine (1 mg) (Atropine Sulfate®, Drogsan, Turkey) was given. Following the administration of drugs into the intrathecal space, blood pressure (systolic, diastolic, mean), heart rate and peripheral Oxygen Saturation (SPO_2) were recorded every 5 min for the first 30 min and then at 15 min intervals throughout the surgery for a total of 2 hrs.

The surgery duration (time from the beginning of surgical incision to the end of the surgery), time to reach the sensory block at the T12 level after spinal anesthesia, time for motor block resolution, first analgesic requirement time, anesthetic complications such as itching, nausea or vomiting and the number of patients requiring epidural medication, ephedrine and atropine during the surgery were recorded.

After the surgery, patients were followed in the recovery room for 120 min. Visual analog scale (VAS; 0 cm = no pain, 10 cm = most severe pain) pain scores at rest, anesthesia-related side effects and sensory block duration were recorded by an independent observer blinded to group assignment at 30 min and 1, 2, 6, 12 and 24 hrs postoperatively. If the patient's VAS was >3, 10 mL of 0.1% bupivacaine solution was administered through the epidural catheter. When the sensory block regressed to the L1 level, the patients were transferred to the ward.

Blood samples (3 cc) for biochemical analysis were taken at preoperative (T0), 2nd hour of surgery (T1) and 24th hour postoperatively (T2). Blood samples were centrifuged at 4000 rpm for 15 min. The obtained serum samples were coded and stored at -80°C until the day of analysis. Serum levels of MDA and HO-1 were measured using the ELISA method with the "Human MDA ELISA Kit" (Cat. No: E1371Hu, BT LAB, China) and "Human HO-1 ELISA Kit" (Cat. No: E0932Hu, BT LAB, China) following the manufacturer's instructions. The MDA and HO-1 concentrations were calculated in nmol/mL and ng/mL, respectively. Additionally, values of CRP (mg/dL), white blood cell count (10^3/mcL), total lymphocyte count (10^3/mcL) and hemoglobin (g/dL) were recorded.

Statistical analysis: A power analysis for the study was calculated using the G*POWER statistical program. The primary objective was the change in serum malondialdehyde, heme oxygenase-1 enzyme and CRP levels. Sample size estimation was based on the study performed by Shukla *et al.*[19]. It was calculated that a total of 78 patients, (26 patients in each group) needed to detect a significant 6-unit difference in CRP levels between the groups at postoperative 24 hrs with a 90% power and a 95% confidence level. Considering potential dropouts during the study, a total of 90 patients, with 30 patients in each group, were included.

The SPSS software 12.0 (SPSS Inc., Chicago, Illinois, USA) was used for the statistical analysis. Numeric data were expressed as mean and standard deviation and categorical data were expressed as count (n) and percentage (%). Kolmogorov-Smirnov test was used to test the normality of the data, a p-value>0.05 is called as normally distributed. One-way Analysis of Variance (ANOVA) was used for statistical analysis if the data followed a normal distribution and the Kruskal-Wallis test was used if the data did not follow a normal. For within-group comparisons of repeated measurements, the ANOVA test was used and for categorical data analysis, the Chi-square test and t-test were utilized. The test results were considered statistically significant when $p<0.05$.

RESULTS

The study was completed with a total of 90 patients, with 30 patients in each group (Fig. 1). The application of CSEA was successful in all patients. No differences were observed interms of demographic characteristics and surgical duration among the study groups (Table 1). There were no statistically significant differences among the groups in terms of mean arterial blood pressure values (p>0.05) (Fig. 2). During the operation, heart rates at 5, 10, 15, 20, 30 and 60 min were observed to be higher in Group 3 compared to Group 2 ($p<0.05$) (Table 2). There were no significant differences among the groups in terms of anesthetic characteristics ($p>0.05$) (Table 3). There were no statistically significant differences among the groups in terms of the number of patients experiencing intraoperative nausea, vomiting or requiring atropine and ephedrine ($p>0.05$) (Table 4). There were no significant differences among groups in terms of postoperative Visual Analog Scale (VAS) values ($p>0.05$) (Table 5).

The serum MDA levels at the 2nd hr of surgery were significantly lower in Group 2 and 3 compared to Group I ($p = 0.001$,$p = 0.002$, respectively). The serum MDA levels at the 24th hr after the operation were significantly lower in Group 2 and 3 compared to Group 1 ($p = 0.000$, for both). The serum HO-1 levels at 2nd hr of surgery were significantly higher in Group 2 and 3 compared to Group 1 ($p = 0.024$, $p = 0.028$, retrospectively). The serum HO-1 levels at the 24th hr after surgery were significantly higher in Group 2 and 3 compared to Group 1 ($p = 0.017$, for both). Groups 2 and 3 had similar serum MDA and HO-1 levels at the 2nd hr of surgery and the 24th hr after surgery (Table 6).

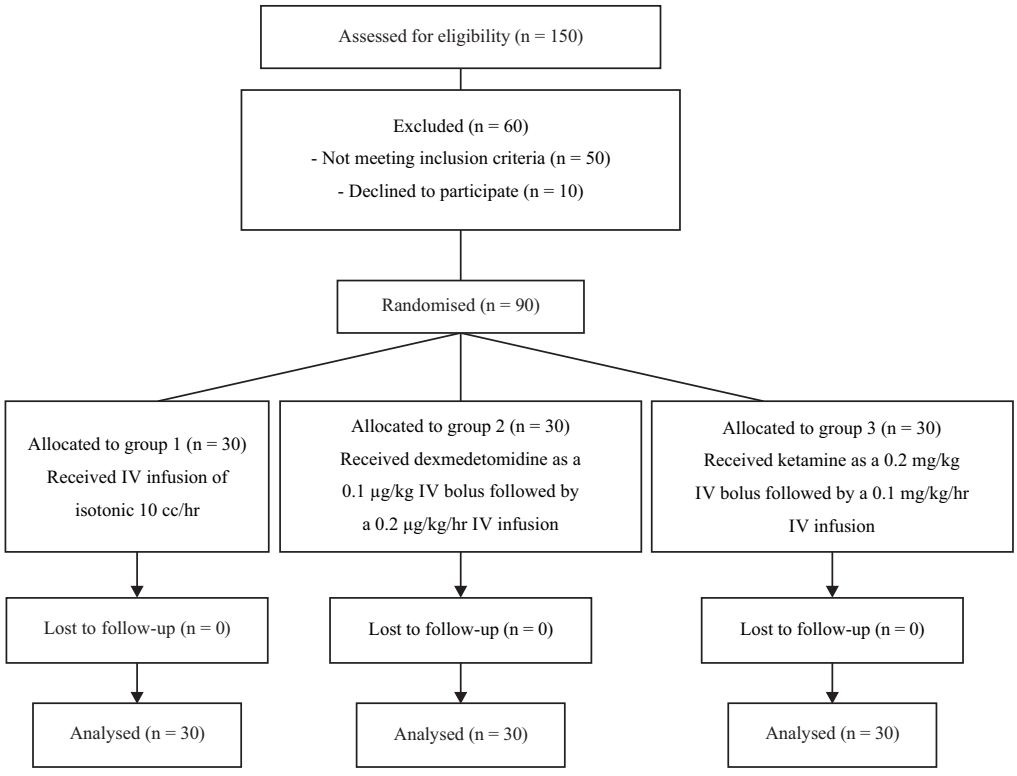

Fig. 1: CONSORT flow diagram for patients included in the study

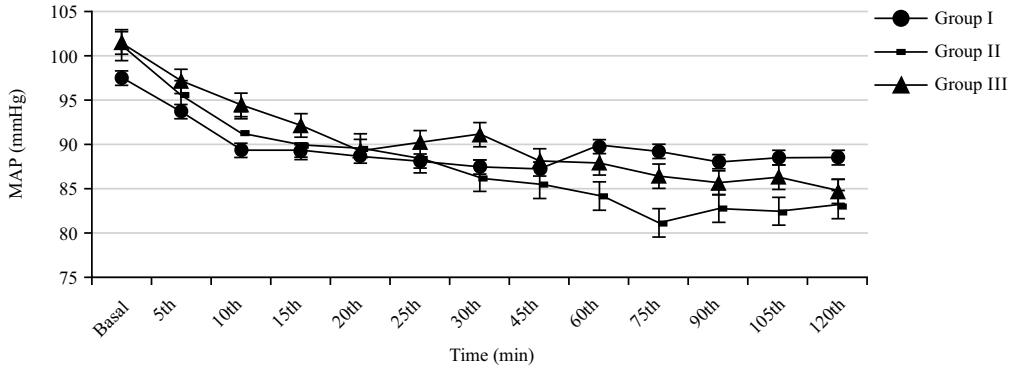

Fig. 2: Changes in mean arterial pressure values during the operation

MAP: Mean arterial pressure

Table 1: Demographic characteristics and operation duration of the groups

Parameter	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	p-value
Age (years)	44.13±14.35	47.57±13.80	41.77±15.53	0.306
Male/female (n)	18/12	20/10	17/13	0.721
Height (cm)	168.10±7.43	171.50±8.88	170.97±7.42	0.210
Weight (kg)	70.93±10.72	75.53±10.13	76.27±9.67	0.095
BMI (kg/m^2)	24.47±2.90	24.91±2.73	25.52±2.49	0.328
Operation duration (min)	117.17±19.46	116.50±26.00	124.83±26.60	0.339
ASA (ASA-I/ASA-II)	17/13	15/15	23/7	0.088
Type of surgery				
THR n (%)	10 (33.3%)	20 (66.7%)	8 (26.7%)	0.853
TKR n (%)	22 (73.3%)	9 (30%)	21 (70%)	

All data are presented as Mean±Standard Deviation or count. ASA: American Society of Anesthesiologists, BMI: Body Mass Index, THR: Total hip replacement and TKR: Total knee replacement

Table 2: Comparison of changes in heart rate during the operation among the groups

Time (min)	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	p-value
Basal value	86.37±11.55	84.43±9.95	86.87±10.96	0.657
5th	83.53±13.95	80.80±12.54	90.33±16.33*	0.034*
10th	83.03±14.53	78.23±12.82	88.87±15.51$^{\lambda}$	0.019*
15th	82.10±16.48	76.17±12.61	85.43±14.53$^{\&}$	0.050*
20th	80.13±15.27	74.10±13.54	86.43±13.48$^{\beta}$	0.004*
25th	78.17±13.31	73.27±12.95	84.07±14.57	0.321
30th	74.17±19.12	71.97±12.82	81.93±14.10$^{\alpha}$	0.038*
45th	77.07±15.12	71.40±14.30	82.77±12.77	0.617
60th	76.67±14.70	71.93±13.52	82.17±12.75$^{\mu}$	0.018*
70th	75.70±13.70	70.50±13.25	78.80±12.44	0.052
90th	77.97±14.59	71.33±12.36	79.10±13.30	0.059
105th	78.57±14.96	72.70±12.71	78.27±12.10	0.163
120th	79.30±14.42	73.07±12.52	79.70±11.26	0.085

All values are given as Mean±Standard Deviation, *p<0.05, *p = 0.012, $^{\lambda}$p = 0.005, $^{\&}$p = 0.016, $^{\beta}$p = 0.001, $^{\alpha}$p = 0.015 and $^{\mu}$p = 0.005; compared to Group II

Table 3: Comparison of data regarding time to reach T12 sensory level, L1 sensory level, time for motor block resolution and time for first analgesic application in the groups

Time (min)	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	p-value
Time to reach T12 sensory level	4.93±3.31	6.03±3.73	6.93±4.74	0.154
Time to regress to L1 sensory level	147.8± 25.78	140.83±27.19	130.5±32.6	0.066
Motor block resolution time	168.33±27.04	161.33±39.03	156.5±43.77	0.469
Time to first analgesic application	164.83±31.25	160.50±33.27	144.67±37.7	0.060

All values are given as Mean±Standard Deviation

Table 4: Comparison of groups in terms of nausea, vomiting and frequency of atropine and ephedrine use

Parameter	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	p-value
Ephedrine n (%)	5 (16.6%)	5 (16.6%)	5 (16.6%)	1.000
Atropine n (%)	0	1 (3.3%)	0	0.364
Nausea-vomiting n (%)	1 (0.03%)	0	1 (0.03%)	0.600

All data are presented as count (n) and percentage (%)

Table 5. Comparison of postoperative VAS (0-10) scores among the groups

Vas score	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	p-value
30th	0.50±1.04	0.83±1.85	0.37±0.92	0.385
60th	0.83±1.36	0.47±1.10	0.57±1.13	0.480
120th	1.10±2.00	1.03±2.04	0.73±1.31	0.708
6th hr	4.03±2.58	3.83±2.37	3.97±2.28	0.948
12th hr	3.57±1.92	3.37±1.79	3.53±2.19	0.915
24th hr	3.73±1.79	4.33±1.76	4.03±1.84	0.440

All values are given as Mean±Standard Deviation. VAS: Visual Analog Scale

Table 6: Comparison of MDA, HO-1, CRP levels and some hematological parameters among the groups

Parameter	Group 1	Group 2	Group 3	p-value
MDA (nmol/mL)				
T0	16.96±14.08	10.55±6.97	14.44±17.20	0.187
T1	15.56±4.35	10.30±5.31$^{\lambda}$	10.49±8.09$^{\mu}$	0.001*
T2	16.44±5.63	8.96±6.28$^{\beta}$	9.10±5.58$^{\beta}$	0.000*
HO-1 (ng/mL)				
T0	1.22±0.55	1.69±1.25	1.52±1.61	0.335
T1	1.04±0.34	1.62±0.92$^{\alpha}$	1.60±1.35$^{\&}$	0.036*
T2	0.94±0.41	1.48±0.77$^{\epsilon}$	1.49±1.21$^{\epsilon}$	0.023*
CRP (mg/L)				
T0	7.71±11.61	15.693±33.03	13.94±17.48	0.360
T1	6.87±10.47	14.043±27.76	11.68±15.76	0.349
T2	85.74±47.17	85.624±60.01	107.69±46.23	0.167
WBC (10^3 mcL)				
T0	8.00±2.31	7.13±2.02	7.29±2.02	0.243
T1	8.61±2.69	8.25±2.69	8.94±3.23	0.647
T2	9.54±2.77	9.83±2.59	9.39±2.40	0.801
Total lymphocyte count				
T0	2.22±0.73	1.93±0.68	2.04±0.74	0.315
T1	1.73±0.57	1.40±0.61	1.512±0.56	0.090
T2	2.45±2.83	1.49±0.56	1.658±0.67	0.075
Hemoglobin (gr/dL)				
T0	13.69±1.93	14.04±2.15	13.88±1.56	0.769
T1	11.81±2.59	12.15±2.17	11.97±2.05	0.846
T2	10.08±2.49	11.89±2.26	11.95±1.03	0.697

All values are presented as Mean±Standard Deviation. T0: Preoperative, T1: 2nd hr of the surgery, T2: 24th hr postoperatively, MDA: Malondialdehyde, HO-1: Heme Oxygenase-1, CRP: C-Reactive Protein, WBC: White Blood Cell, *p<0.05, $^{\lambda}$p = 0.001, $^{\mu}$p = 0.002, $^{\beta}$p = 0.000, $^{\alpha}$p = 0.024, $^{\&}$p = 0.028 and $^{\epsilon}$p = 0.017, compared with Group I

DISCUSSION

In this study, the effect of IV dexmedetomidine and ketamine during surgery on postoperative oxidative stress markers including serum CRP, MDA and HO-1 enzyme levels were investigated in patients undergoing lower extremity surgery under CSEA. Serum MDA levels at the 2nd hr of surgery and the 24th hr postoperatively were similar in patients receiving dexmedetomidine and ketamine and they were lower in both groups compared to the control group. Serum HO-1 levels at the 2nd hour of surgery and the 24th hour postoperatively were similar in patients receiving dexmedetomidine and ketamine and they were higher in both groups compared to the control group.

Modern anesthesia techniques are designed to minimize stress responses during surgery. Dexmedetomidine, a selective alpha-2 agonist drug, has been shown in studies to have sympatholytic, analgesic and sedative effects and reduce neuroendocrine and hemodynamic responses associated with surgery and anesthesia[12,13]. Ketamine, a phencyclidine derivative, is a general anesthetic used for sedation due to its minimal negative effects on the cardiac and respiratory systems[14]. Koyuncu *et al.*[20] investigated the effects of dexmedetomidine and ketamine used in addition to epidural

anesthesia on sedation quality and postoperative pain in patients undergoing lower extremity surgery. They reported that systolic and diastolic blood pressure values at the 45th and 105th min of the operation were lower in the dexmedetomidine group compared to the ketamine group. They also reported that the first analgesic application time within the first 4 hrs postoperatively, the need for additional analgesics, the amount of antiemetic consumption and pain scores were lower in the dexmedetomidine group. In this current study, heart rate was higher in the ketamine group at 5, 10, 15, 20, 30 and 60 min during the operation compared to the dexmedetomidine and control groups. There were no differences between the groups in terms of intraoperative nausea, vomiting frequency, atropine and ephedrine use. The reason for these different results may be attributed to methodological differences in the studies. While CSEA applied to the cases in the current study, Koyuncu *et al.*[20] applied only epidural anesthesia. Additionally, in the current study, dexmedetomidine was administered at a dose of 0.1 µg/kg IV bolus followed by an infusion of 0.2 µg/kg/hr and ketamine was administered at a dose of 0.2 mg/kg bolus followed by an infusion of 0.1 mg/kg/hr throughout the operation. Shukla *et al.*[19] used dexmedetomidine at a dose of 0.5 µg/kg/hr infusion and ketamine at a dose of 0.5 mg/kg/hr infusion. The differences in both drug dosages used and the regional anesthetic method can explain the discrepancies in the results.

The MDA is a reactive oxygen species formed as a result of the oxidation of cell membrane lipids. Saricaoglu *et al.*[21] investigated the effect of ketamine sedation on oxidative stress in patients undergoing arthroscopic knee surgery under spinal anesthesia with a tourniquet. They reported that patients who received ketamine infusion at a rate of 0.5 mg/kg/hr during the operation had lower levels of MDA and hypoxanthine in serum and synovial membrane tissue samples compared to the placebo group. They concluded that ketamine sedation reduced lipid peroxidation markers. In a similar study, Koruk *et al.*[22] investigated the effect of dexmedetomidine administered by IV infusion at a rate of 0.3-0.5 µg/kg/hr and ketamine at a rate of 1-1.5 mg/kg/hr on total antioxidant status (TAS), total oxidant status (TOS) and MDA levels, which indicate ischemia-reperfusion injury and oxidative stress response in patients undergoing arthroscopy under spinal anesthesia. They found no differences between the groups in terms of TAS, TOS and MDA values. A study by Maier *et al.*[23] demonstrated that dexmedetomidine is effective in protecting against focal ischemia and oxidative stress in rabbits. Consistent with these results, this present study reported a significant decrease in serum MDA levels at the 2nd hour of surgery and 24 hrs after the operation with ketamine and dexmedetomidine infusion. Considering the sedative-anxiolytic properties, these results suggest that IV administration of dexmedetomidine or ketamine during the operation may be effective in reducing oxidative stress.

Heme oxygenase-1, unlike other HO isozymes, is a 'heat-shock' protein and functions as a stress response protein that increases with various stress factors. The HO-1 is primarily known for its anti- apoptotic, anti-proliferative, anti-thrombotic and vasodilatory effects[24]. Additionally, HO- 1 is an enzyme with strong anti-inflammatory properties and antioxidant properties known to protect tissues from stress and injuries[25]. In a study by Gao *et al.*[26], during single lung ventilation, it was shown that the expression level of HO-1 in lung tissue was significantly higher in patients where dexmedetomidine infusion was initiated compared to the control group. This suggests a protective role of dexmedetomidine against inflammatory and oxidative stress reactions by increasing HO-1 expression. In another study, Suliburk *et al.*[27] hypothesized that HO-1 might be associated with ketamine's potent hepatoprotective properties. In mice with endotoxin-induced liver injury under anesthesia with isoflurane and ketamine, they reported that serum HO-1 levels were statistically significantly higher in the ketamine group. Consistent with these results, this current study reported that postoperative HO-1 values were higher in the groups where we administered ketamine and dexmedetomidine infusion compared to the control group.

The literature contains studies investigating the antioxidant effects of ketamine and dexmedetomidine in surgical patients. However, there is no study comparing the antioxidant effects of both drugs in patients undergoing the same surgery. In this regard, our study is original and important in providing a new contribution to the literature. One limitation of the present study is that different doses of both drugs were not compared. New studies comparing the antioxidant effects of both low and high doses of the drugs may be planned.

CONCLUSION

In the present study, the effects of dexmedetomidine and ketamine administered via IV infusion after the loading dose on serum MDA, a marker of oxidative stress and serum HO-1, a marker of the antioxidant system, were similar in patients undergoing lower extremity surgery under CSEA. In appropriate cases, both agents can be used as sedatives and anxiolytics to reduce neuroendocrine stress responses associated with surgery and anesthesia.

SIGNIFICANCE STATEMENT

This prospective, double-blind, randomized controlled trial was designed to compare the effects of intravenously administered dexmedetomidine and ketamine on serum malondialdehyde (MDA) and Heme Oxygenase-1 (HO-1) levels in patients undergoing lower limb surgery with combined spinal epidural anesthesia. Serum MDA and HO-1 levels were found to be similar in both groups. Both agents can be used as sedatives and anxiolytics to reduce neuroendocrine stress responses associated with surgery and anesthesia. The study recommended that the use of either drug as an adjuvant in a multimodal management strategy during operations may be effective in reducing postoperative morbidity associated with surgical stress.

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