

The effects of ketamine and lidocaine on free radical production after tourniquet-induced ischemia-reperfusion injury in adults

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ABSTRACT

BACKGROUND: The primary aim of this study was to compare the effects of a small-dose infusion of 2 antioxidant agents, ketamine and lidocaine, on ischemia-reperfusion injury (IRI) in patients undergoing elective lower limb surgery. Ischemia-modified albumin (IMA), lactate, and blood gas levels were all measured and assessed.

METHODS: A total of 100 patients who underwent lower extremity surgery were randomized into 3 groups. After spinal anesthesia, the ketamine group (Group K, n=33) was given a ketamine infusion, a lidocaine infusion was administered to the lidocaine group (Group L, n=33), and in the control group (Group C), 0.9% a sodium chloride infusion was performed. Blood samples were obtained for IMA analysis before anesthetic administration (baseline), at 30 minutes of tourniquet inflation (ischemia), and 15 minutes after tourniquet deflation (reperfusion). Arterial blood gas measurements were determined before anesthetic administration and 15 minutes after tourniquet deflation.

RESULTS: The lactate and IMA levels at reperfusion were significantly lower in both the ketamine group and the lidocaine group when compared with the control group.

CONCLUSION: The administration of both ketamine and lidocaine infusions significantly decreased skeletal muscle IRI-related high lactate and IMA levels. These results suggest the possibility of the clinical application of ketamine or lidocaine infusions in cases of skeletal muscle-related IRI.

Keywords: Ischemia reperfusion injury; ketamine; lidocaine.

INTRODUCTION

Tourniquet placement is often used in limb surgery to provide bloodless field and control intraoperative bleeding.^[1] Metabolic tissue alterations, such as decreased levels of phosphocreatine, increased lactate, increased glycogenolysis, decreased pH, and increased production of reactive oxygen species (ROS), are seen during tourniquet at ischemia and reperfusion periods known as the ischemia-reperfusion injury (IRI).^[1,2] The consequences of such injury are local and remote tissue destruction, and sometimes death. A variety

of markers have been proposed to evaluate IRI and strategies including anesthetic-agent-induced protection to attenuate skeletal muscle injury, but none have been incorporated into routine clinical management.^[3]

Ischemia, hypoxia, and ROS can generate the highly reactive hydroxyl radical, which results in site-specific modification to the N-terminus of the albumin moiety, especially at the N-Asp-Ala-His-Lys sequence, thereby producing ischemia-modified albumin (IMA).^[4] Recently, IMA, a novel ischemia-associated biomarker, was introduced to assess oxidative stress^[5]

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in a number of acute ischemic conditions, such as skeletal muscle ischemia due to a pressurized tourniquet cuff, cerebral, myocardial, renal, mesenteric, and pulmonary infarct or ischemia.^[4-6]

Ketamine, an N-methyl-D-aspartate antagonist, is a dissociative anesthetic agent that was found to attenuate IRI-induced lipid peroxidation in various tissues, such as brain, myocardium, and skeletal muscle.^[7-9] Lidocaine has been reported to attenuate the IRI injury^[10] and the I/R-induced inflammatory response.^[11] So far there is no study that compared the effect of these two agents on tourniquet-induced skeletal IRI injury.

In this randomized, prospective, and double-blind study, our primary aim was to compare the effects of small-dose infusion of two antioxidant agents, ketamine and lidocaine, on IRI in patients undergoing elective lower limb surgery in an early short time period. For this purpose, IMA, lactate, and blood gas levels were all measured.

MATERIALS AND METHODS

The local ethics committee of Necmettin Erbakan University School of Medicine approved the study (29.05.2009/227), and written informed consent was obtained from the included patients who were admitted to orthopedics and traumatology department for arthroscopic knee surgery. One hundred consecutive American Society of Anesthesiologist Grade I and II^[12] patients undergoing arthroscopic knee surgery were enrolled in this study by using computer-generated randomization list. Patients with metabolic, renal, or hepatic disturbances; those with a recent history of any antioxidant drug use or a history of chronic pain; those with body mass index (BMI) over 30 kg/m²; those with congestive cardiac failure, intraoperative blood transfusions, hypothermia, or hyperthermia; and those who were allergic to local anesthetics were excluded from the study.

Before spinal block, midazolam 0.03 mg/kg was intravenously administered to all patients. For all patients, spinal anesthesia was performed with 12.5 mg bupivacaine. The patients were randomly assigned into three groups by computer-generated random numbers: after spinal anesthesia, in the ketamine group (Group K, n=33), ketamine infusion at 0.5 mg/kg/h after a 0.5 mg/kg bolus; in the lidocaine group (Group L, n=33), lidocaine infusion at 0.6 mg/kg/h after a 1 mg/kg bolus; and in the control group (Group C, n=34), 0.9% NaCl infusion at 0.6 mg/kg/h after a 0.5 mg/kg bolus. The tourniquet was applied at a pressure approximately twice the systolic arterial blood pressure (nearly 250–300 mmHg). During the operation, the fluid deficits were corrected with normal saline.

For each patient, tourniquet time, duration of the surgical intervention, and anesthetics infusion period were recorded. The Ramsey Sedation Scale (RSS)^[13] [1= anxious and agitated,

2= cooperative and tranquil, 3= drowsy but responsive to command, 4= asleep but responsive to glabellar tap, 5= asleep with a sluggish response to tactile stimulation, 6= asleep and no response] was used to measure sedation before and at 5, 10, 20, 30, 40, 60, and 80 min after administration. Systolic blood pressure (SBP), diastolic blood pressure (DBP), peripheral oxygen saturation (SpO₂), and heart rate (HR) were also recorded. Sequential venous blood samples were obtained from the antecubital vein of the arm. The dorsal vein of the other hand was used for intravenous fluid, and ketamine and lidocaine infusions. Samples for blood gas analysis were taken from the insertion of radial arterial cannula. Blood gas analysis was performed on the RapidLab 860 series (Bayer Diagnostics, USA). Arterial blood gas measurements were determined before administration of anesthetics and 15 min after tourniquet deflation. Lactate concentrations were expressed in mmol/L.

Blood samples for IMA analysis were obtained before administration of anesthetics (baseline), at 30 min of tourniquet inflation (ischemia), and 15 min after tourniquet deflation (reperfusion). The serum and plasma samples were prepared with 15 min of centrifugation at 3000 rpm. The specimens were stored at -80°C till the time of analysis. The serum IMA level was analyzed using the rapid and colorimetric method described by Bar-Or et al.^[14] This is based on the principle of quantitative scanning of free cobalt present after cobalt binding has taken place. The IMA results were expressed in absorbance units (ABSU).

Perioperative potential side effects, such as nausea, vomiting, and dysphoria (including hallucinations and dreams), confusion, dizziness, false or unusual sense of well-being, were recorded.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (the SPSS program for Windows-Version 20.0; IBM Corporation, Armonk, NY, USA). Data were analyzed for the compliance with normal distribution. In the inter-group comparisons in statistically independent samples, T-test and one-way ANOVA test was performed on parametric data complying with the normal distribution. Post-hoc tests were performed using Tukey's test. The Kruskal–Wallis H and Mann–Whitney U tests were performed on nonparametric data, and the chi-square test was performed on nominal data. The value of p<0.05 was considered statistically significant.

RESULTS

Of 102 patients who were admitted to orthopedics and traumatology department of Necmettin Erbakan University Meram Faculty of Medicine, 100 patients were enrolled in the study (Fig. 1). Two patients were excluded from the study because of needed general anesthesia. Eligible patients were divided into three groups, and the different drugs were given infusion.

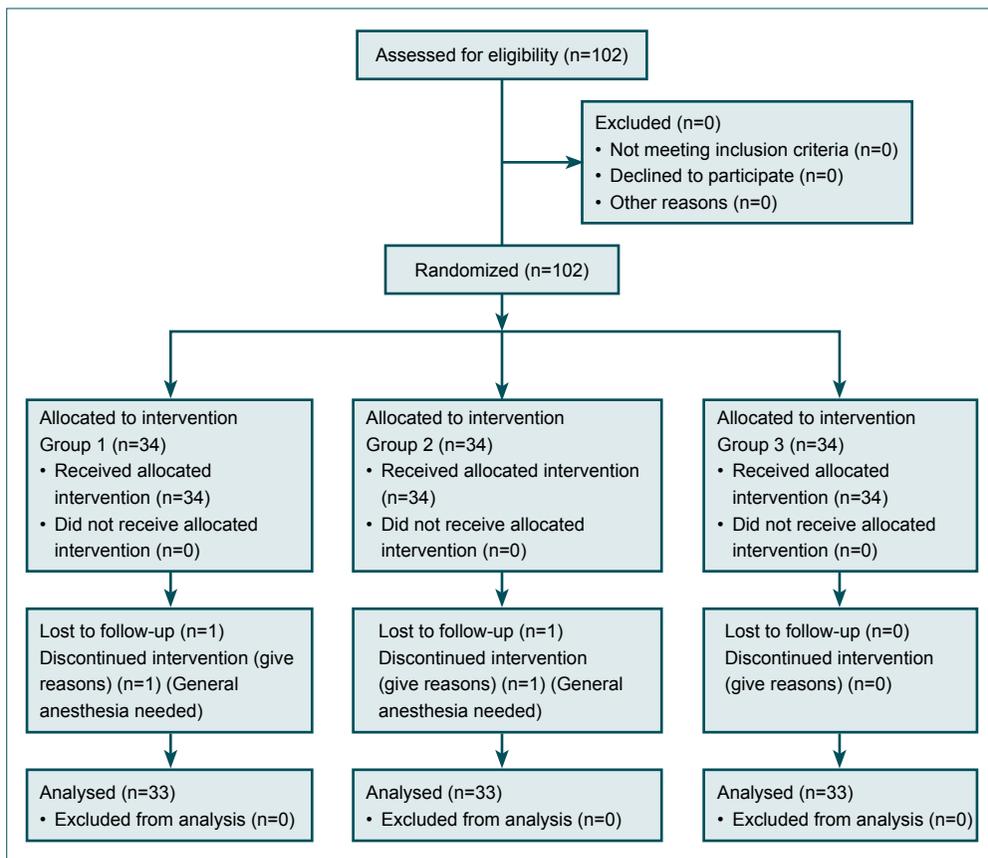


Figure 1. CONSORT flow diagram (Group 1, Ketamine; Group 2, Lidocaine; Group 3, Control).

There were no significant differences among the groups in demographic data (Table 1). No statistically significant differences were observed in the intragroup comparisons as regards SBP, DBP, and HR (Table 2). The RSS scores of the ketamine group were higher than those of the other groups ($p=0.01$). Maximum sedation scores were 4 (8 of 33 patients), 2 (28 of 33 patients), and 2 (25 of 34 patients) in ketamine, lidocaine, and control groups, respectively (Table 3).

Patients arterial lactate levels and IMA levels were presented in Figures 2 and 3. The lactate levels of patients were signifi-

cantly lower in both ketamine and lidocaine groups (the mean lactate levels were 1.62 ± 0.90 for ketamine group, 1.37 ± 0.54 for lidocaine group, 1.91 ± 0.80 for control group; and $p=0.01$ and $p=0.01$, respectively), and the IMA levels at reperfusion were significantly lower in both ketamine and lidocaine groups (the mean IMA levels were 0.407 ± 0.100 for ketamine group, 0.447 ± 0.100 for lidocaine group, 0.497 ± 0.091 for control group; and $p=0.000$ and $p=0.037$, respectively) when compared with the control group (Figs. 2 and 3). No nausea, vomiting and dysphoria, confusion, dizziness, false or unusual sense of well-being were recorded.

Table 1. Patient demographics, values are presented as mean±standard deviation

	Ketamine group (n=33)	Lidocaine group (n=33)	Control group (n=34)
Age (years)	42±12	44±14	43±16
Sex (female/male)	12/21	13/20	11/23
Body mass index (kg/m ²)	25±2	25±3	25±3
ASA status (I/II)	18/15	19/14	18/16
Tourniquet time (min)	66.6±4	66.0±4.10	66.6±3
Surgery duration (min)	65.1±4	64.3±4	64.4±4
Anesthetics infusion duration (min)	81.9±3	82.1±3	82.3±3

ASA: American Society of Anesthesiologists.

Table 2. Hemodynamics of patients (mean±standard deviation)

	Baseline	t1	t2
	Mean±SD	Mean±SD	Mean±SD
Heart rate (bpm)			
Ketamine group	76.76±13.19	72.24±13.22	73.48±12.05
Lidocaine group	79.12±13.21	66.94±13.50	67.79±11.58
Control group	76.38±10.14	66.91±10.57	67.82±11.08
Systolic blood pressure (mmHg)			
Ketamine group	134.21±14.49	131.67±13.81	132.70±13.07
Lidocaine group	134.70±17.27	125.24±13.61	125.48±15.42
Control group	135.85±16.24	124.85±13.75	124.68±19.16
Diastolic blood pressure (mmHg)			
Ketamine group	81.88±8.72	81.09±11.90	80.88±10.28
Lidocaine group	79.36±12.90	76.67±12.42	76.24±12.39
Control group	83.35±10.20	75.47±10.98	74.85±11.93

t1: Ischemia period; t2: Reperfusion period; SD: Standard deviation.

Table 3. Ramsey Sedation Scale (RSS) scores of the groups. P=0.00 in the ketamine group when compared with lidocaine and control group

Time (RSS scores)	Ketamine group (n=33), n	Lidocaine group (n=33), n	Control group (n=34), n
5 min. (1/2/3/4/5/6)	0/8/17/8/0/0	19/14/0/0/0/0	22/12/0/0/0/0
10 min. (1/2/3/4/5/6)	0/9/19/5/0/0	16/17/0/0/0/0	20/14/0/0/0/0
20 min. (1/2/3/4/5/6)	1/13/18/1/0/0	8/25/0/0/0/0	10/24/0/0/0/0
30 min. (1/2/3/4/5/6)	1/18/12/2/0/0	5/28/0/0/0/0	11/23/0/0/0/0
40 min. (1/2/3/4/5/6)	1/18/13/1/0/0	7/26/0/0/0/0	15/19/0/0/0/0
60 min. (1/2/3/4/5/6)	1/18/13/1/0/0	10/23/0/0/0/0	17/17/0/0/0/0
80 min. (1/2/3/4/5/6)	1/18/12/2/0/0	11/22/0/0/0/0	18/16/0/0/0/0

RSS: 1= anxious and agitated, 2= cooperative and tranquil, 3= drowsy but responsive to command, 4= asleep but responsive to glabellar tap, 5= asleep with a sluggish response to tactile stimulation, 6= asleep and no response.

DISCUSSION

Our main finding was that 66 min of lower limb tourniquet ischemia causes a significant change in serum lactate and IMA levels in reperfusion period, which was attenuated by IV infusion of ketamine and lidocaine. But there were no statistically significant differences between the ketamine and lidocaine groups. In the ischemia period, infusion of ketamine but not lidocaine statically attenuated the increase in IMA levels. Tourniquet causes several metabolic changes during application and release of the extremity. The damage caused during ischemia is called “ischemic injury”. Although reperfusion means a termination of ischemia and is essential for the cell to survive and to restore normal function, it paradoxically causes damage to the cell; this injury is called “reperfusion injury”. The term “ischemia–reperfusion injury” is also used

to represent both types of damage together.^[15] The risk of revascularization in ischemic extremities may result to reperfusion injury that develops on remote organs such as lungs, heart, liver, and kidneys that threaten life and makes progress acute renal and respiratory failure, cardiac dysfunction, and even death.^[16–18]

After release of tourniquet, the toxic products of the anaerobic metabolism in the ischemic limb enter the systemic circulation.^[19] Since the blood circulation and oxygen delivery to the tissues decrease, the cellular metabolism supplies the required energy from anaerobic glycolysis, which is an alternative source for ATP genesis during hypoxia or anoxia. Anaerobic glycolysis produces lactate and depletes glycogen. The accumulation of lactate, a product from anaerobic metabolism, was used as an indirect index of ischemia in this

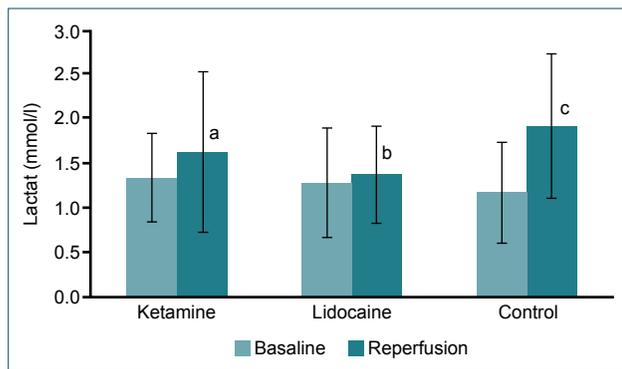


Figure 2. Lactate levels of patients. ^ap=0.02 for lactate in ketamine group compared with the control group. ^bp=0.001 for lactate in lidocaine group compared with the control group. ^cp=0.015 when compared with baseline levels of control groups.

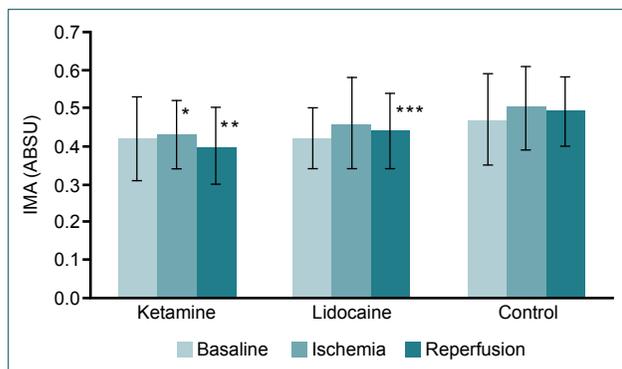


Figure 3. The IMA levels of patients. *p=0.015 for IMA at ischemia period in ketamine group compared with the control group. **p=0.001 for IMA at reperfusion period in ketamine group compared with the control group. ***p=0.03 for IMA at reperfusion period in lidocaine group compared with the control group. IMA: Ischemia-modified albumin; ABSU: Absorbance units.

study. The serum lactate level in the control group (but not ketamine and lidocaine group) was found to be significantly higher in reperfusion period than the basal levels, which was consistent with the literature.^[19] The lactate levels in lidocaine and ketamine groups in the reperfusion period were found significantly lower than that in the control group. This study suggests that the reduced lactate production may contribute to the beneficial effects of lidocaine and ketamine. However, increase of lactate in control group did not exceed the clinically acceptable abnormal value in patients (<2 mmol/L).^[19]

Studies performed in in-vitro experiments conducted with bovines, ketamine had reportedly inhibited lipid peroxidation.^[20] Protective effects of ketamine against neuronal IRI may be attributed to its NMDA receptor antagonistic activity leading to blockade of calcium influx.^[21] In this study, the result of the lower levels of IMA in ischemia period suggests that ketamine decreases the ischemic damage that begins with the increase of calcium influx from the damaged endoplasmic reticulum while trying to provide intracellular ion balance in the ischemic period by blocking intracellular calcium uptake.

And the significance difference in reperfusion period between the control group and the ketamine group suggests that ketamine minimizes IRI, and this causes destructive changes by enhancing blood influx into affected target tissue. In many studies, ketamine's effects on IRI were evaluated with different biomarkers.^[8,22]

Saricaoglu et al.^[8] studied the effect of ketamine sedation on oxidative stress during arthroscopic knee surgery with tourniquet application by determining blood and tissue malonyldialdehyde (MDA) and hypoxanthine (HPX) levels, and they concluded that ketamine sedation attenuates lipid peroxidation markers. In this study, the inexpensive ischemic early detection sensitive biomarker IMA was analyzed; and in both ischemia and reperfusion period, ketamine exert protective effects on skeletal IRI. The protective effects of ketamine on skeletal IRI may be accomplished by mechanisms interfering with ROS because of the ROS developing very important structural disorders in proteins.

In cardiology, prevention of arrhythmia and reduction of infarct area can be achieved with lidocaine. Furthermore, local anesthetics inhibit migration, enzyme release, and O₂ generation of polymorphonuclear leukocytes. Study performed on animal models of IRI had also manifested its cardioprotective effects.^[23] Myocardial infarct area diminishes by 25%–30% in canine models that received lidocaine infusion 90 min before induction of ischemia.^[23] In another experimental study, the effect of lidocaine administration during ischemia and reperfusion had beneficial effects on smooth muscle motility. Initiating lidocaine treatment during surgery to treat colic in horses may improve lidocaine's prokinetic features by protecting smooth muscles from effects of ischemia and reperfusion injury.^[10] Yet no clinical trial has been studied before that investigated the effect of lidocaine on tourniquet-induced IRI. Hence in this study, the new ischemia biomarker, IMA, was analyzed during both ischemia and reperfusion period. The lower level of IMA in reperfusion process suggests that lidocaine exerts a scavenging action on free radical processes. The results were similar in the lidocaine and in the control groups during ischemia period. This is also thought us that lidocaine has no direct effect on the polymorphonuclear leukocyte activation in the phase of ischemia. Similarly, the study investigated the effect of lidocaine on brain lipid peroxidation, as reflected by jugular vein malondialdehyde concentrations, and of polymorphonuclear leukocyte activation in peripheral venous blood samples following transient global cerebral ischemia.^[24] In the study conducted by Lantos et al.,^[24] the lidocaine administration did not prevent the elevation of the malondialdehyde concentrations during ischemia. In this study, since the lipid peroxidation products have not been analyzed, we cannot say anything about lidocaine's efficacy at this point.

The N-terminal end of human serum albumin, which is a temporary binding site for divalent forms of metals, alters after

exposure to oxidative stress and/or ischemia; and it forms the variant form of human serum albumin, IMA.^[25] Prolonged leg ischemia caused by tourniquet during lower extremity surgery or because of arterial clamping during major vascular surgery resulted an increase in serum IMA concentrations.^[5,26] In this study, the IMA levels in both ketamine and lidocaine groups were lower than those in the control group in the reperfusion period. As both MDA and IMA increase in limb surgery in which tourniquets are used, Erturk et al.^[27] employed these as a marker of IRI in their study.

The side effects of ketamine (hallucinations, fearful dreams) were well known. In this study, premedication with midazolam, which is known to prevent from these effects, was administered to all patients in the study group, similar to Saricaoglu et al.'s^[8] study.

When the hemodynamic data were evaluated, statistical differences regarding SBP, DBP, and HR were found. Ketamine group had high HR, SBP, and DBP compared to the lidocaine and control group. These indirect cardiovascular effects are due to central stimulation of the sympathetic nervous system and inhibition of the reuptake of norepinephrine after release at nerve terminals.^[28] But no significant changes were seen in the vital signs of the patients. The RSS in the ketamine group was higher in a clinically acceptable level as compared to the lidocaine and control groups ($p < 0.05$).

There were some limitations of this study. First, we had blood samples from only 15 min after the tourniquet was released. Thus, we did not know the patients' metabolic status in the late postoperative period. Moreover, our tourniquet time was approximately 66 min. Acidosis and base deficit resulting from IRI may be more evident in some procedures with longer tourniquet times. Secondly, most of the patients in this study had ASA I-II, and thus the present patient population did not comprise all of the scenarios in which has preoperative high risk. The IRI affects the endogenous antioxidant system. The endogenous antioxidant enzyme concentrations (like superoxide dismutase, glutathione peroxidase) decreased below normal levels in the acute period following ischemic injury. Hence, the effect of ROS increases. However, we did not measure the levels of any endogenous antioxidant enzyme at proper times of IRI. In further studies, it will be worthy to measure endogenous antioxidant enzyme levels with the markers of IRI simultaneously. Finally, IMA is a new biomarker, which is significantly influenced by a wide array of physiologic variables, including exercise and hydration. We were not able to control all of the variables that could possibly influence IMA levels.

In conclusion, administration of both the ketamine and lidocaine infusion significantly decreased skeletal-muscle-IRI-related high lactate and high IMA levels. These results suggest the possibility of clinical application of ketamine or lidocaine infusions induced by skeletal-muscle-related IRI. Different

dosages, alternate combination of drugs, and markers should be investigated in future studies to evaluate the mechanism.

Acknowledgment

There is no conflict of interest. The institutional sources were used for this study.

Conflict of interest: None declared.

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ORIJİNAL ÇALIŞMA - ÖZET

Ketamin ve lidokainin erişkinlerde turnike kaynaklı iskemi-reperfüzyon hasarından sonra serbest radikal üretimi üzerine etkileri

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AMAÇ: Amacımız, elektif alt ekstremitte cerrahisi uygulanan hastalarda iki antioksidan ajan, ketamin ve lidokainin küçük doz infüzyonunun iskemi-reperfüzyon hasarı (IRI) üzerine olan etkisini karşılaştırmaktır. Bu amaçla iskemi modifiye albümin (IMA), laktat ve kan gazı seviyeleri ölçüldü.

GEREÇ VE YÖNTEM: Alt ekstremitte cerrahisi uygulanan 100 hasta randomize olarak üç gruba ayrıldı. Spinal anesteziden sonra ketamin grubunda (Grup K, n=33), ketamin infüzyonu, lidokain grubunda (Grup L, n=33), lidokain infüzyonu, kontrol grubunda (Grup C) %0.9 NaCl infüzyonu uygulandı. IMA analizi için kan örnekleri anestezik uygulamadan önce (bazal değer), 30 dakika turnike enfstasyonunda (iskemi) ve turnike deflasyonundan 15 dakika sonra (reperfüzyon) elde edildi. Arteriyel kan gazı ölçümleri anestezik uygulaması öncesi ve turnike deflasyonundan 15 dakika sonra belirlendi.

BULGULAR: Reperfüzyonda laktat ve IMA düzeyleri kontrol grubu ile karşılaştırıldığında hem ketamin grubunda hem de lidokain grubunda anlamlı olarak düşüktü.

TARTIŞMA: Hem ketamin hem de lidokain infüzyonunun uygulanması, iskelet kası IRI ile ilişkili yüksek laktat ve yüksek IMA düzeylerini anlamlı olarak azaltmıştır. Bu sonuçlar, iskelet kası ile ilişkili IRI'da, ketamin veya lidokain infüzyonlarının klinik uygulanabilme olasılığını düşündürmektedir.

Anahtar sözcükler: İskemi reperfüzyon hasarı; ketamin; lidokain.

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