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Original Contribution

The effects of a small-dose ketamine-propofol combination on tourniquet-induced ischemia-reperfusion injury during arthroscopic knee surgery☆

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Abstract
Study Objective: To determine the effects of a small-dose ketamine-propofol combination used for sedation during spinal anesthesia on tourniquet-induced ischemia-reperfusion injury.
Study Design: Prospective randomized study.
Setting: Training and research hospital.
Patients: 60 adult, ASA physical status 1 and 2 patients, ages 20–60 years, scheduled for elective arthroscopic knee surgery for meniscal and chondral lesions.
Interventions: The initial hemodynamic parameters were recorded and blood samples were collected at baseline (T1); then spinal anesthesia was performed. In Group I (n=30), a combination of 0.5 mg/kg/hr of ketamine and 2 mg/kg/hr of propofol was administered; Group II (n=30) received an equivalent volume of saline as an infusion. A pneumatic tourniquet was applied.
Measurements: Malondialdehyde (MDA), superoxide dismutase (SOD), and catalase levels were measured one minute before tournique deflation in the ischemic period (T2), then 5 (T3) and 30 (T4) minutes following tourniquet deflation in the reperfusion period.
Main Results: No differences were noted between groups in hemodynamic data ($P > 0.05$) or SOD levels ($P > 0.05$). In Group I, MDA levels at T2 were lower than in Group II ($P < 0.05$). In Group I, catalase levels were lower at T2 and T4 than they were in Group II ($P < 0.05$).
Conclusion: Small-dose ketamine-propofol combination may be useful in reducing tourniquet-induced ischemia-reperfusion injury in arthroscopic knee surgery.

1. Introduction

Tourniquet application has gained widespread use during orthopedic surgery to reduce blood loss [1]. After the ischemic period, blood flow is necessary both for renewal

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of cells and clearance of the accumulated toxic metabolites [2]. When the tourniquet is released, excessive formation of reactive oxygen species (ROS) causes peroxidation of membrane lipids [3]. This process triggers oxidation of the polyunsaturated fatty acids, destroying membrane structures and producing toxic metabolites such as malondialdehyde (MDA) [4–6]. This process is defined as ischemia-reperfusion injury. Orthopedic surgery with a tourniquet is a good human model for ischemia-reperfusion injury [2].

There are several defense mechanisms against ischemia-reperfusion injury in the body. Endogenous enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH) play a part in the defense mechanisms of the body in normal conditions by removing ROS effectively. They are overwhelmed during ischemia and subsequent reperfusion when a large amount of free radicals are rapidly produced [7,8]. Some specific agents have been used to prevent the effects of ischemia-reperfusion injury. Certain anesthetics, particularly potent inhalational and intravenous (IV) anesthetics afford protection against ischemia-reperfusion injury [9]. Propofol (2,6-diisopropyl-phenol) is chemically similar to phenol-based free-radical scavengers. The concentration of propofol required for a preventive effect on free-radical formation varies on the basis of different experimental methods [5]. Large concentrations (much larger than the anesthetic level) of propofol prevent free-radical production [10]; lower doses of propofol also prevent the production of free radicals [5]. Ketamine, a dissociative anesthetic, protects neurons against ischemia-reperfusion-induced lipid peroxidation. Sedation with ketamine attenuates lipid peroxidation markers in arthroscopic knee surgery with tourniquet application [11].

The ketamine-propofol combination has been used for sedation in regional anesthesia, but no clinical data are available on its use in ischemia-reperfusion injury. In this study, we aimed to examine the effects of a combination of small-dose ketamine-propofol on tourniquet-induced ischemia-reperfusion injury by examining levels of MDA, SOD, and catalase.

2. Materials and methods

This study was approved by the local Ethics Committee of Numune Training and Research Hospital, Ankara. Turkey. Sixty ASA physical status 1 and 2 patients, age 20 to 60 years, who were candidates for elective arthroscopic knee surgery for meniscal and chondral lesions were included in this prospective randomized study. Participants provided written, informed consent to participate in the study. Patients were randomized to two groups by the sealed envelope method. Exclusion criteria were hypersensitivity to the agents used in the study, neuromuscular diseases, psychiatric disorders, bone deformities such as scoliosis and rheumatoid arthritis, infections or chronic skin diseases, antioxidant drug intake history, and morbid obesity.

During the preoperative evaluation, patients were informed about the anesthetic method they were to receive. In the operating room, vascular access was obtained. A comprehensive anesthesia monitor (CAMS II) was used for monitoring electrocardiogram (ECG), heart rate (HR), and systolic (SBP), diastolic (DBP), and mean (MAP) arterial pressures via automatic noninvasive method. Peripheral oxygen saturation (SpO_2) was monitored by pulse oximetry. The initial hemodynamic parameters of the two groups were recorded. Infusion of 0.9% NaCl solution was started. On the dorsum of the other hand, vascular access was established for collection of blood samples. Blood samples were drawn for evaluation of the preischemia values (T1). After having the patients sit up straight, the subarachnoid space was entered through L_3-L_4 by a 22-gauge Quincke spinal needle. Spinal anesthesia was performed in both groups by administration of 12.5 mg of 0.5% hyperbaric bupivacaine (5 mg/mL heavy Marcaine). Patients were then placed supine; in Group I (n=30), 0.5 mg/kg/hr of ketamine and 2 mg/kg/hr of propofol combination was infused intravenously, and in Group II (n=30) the equivalent volume of saline was infused. Patients were given nasal oxygen at the rate of 2 L/min by nasal canula.

A pneumatic tourniquet was applied to the relevant extremity. When the level of sensory blockade reached Th12, the tourniquet pressure was raised twice as much as the MAP measured during the preoperative period. Sensory block was assessed by pinprick test in both extremities at the 5^{th} and 10^{th} minutes after the injection. In cases where the level of sensory blockade did not reach the Th12 level in 10 minutes following spinal injection, the block was assessed to be unsuccessful and those patients were excluded from the study. The Ramsay Sedation Scale (RSS; 1=anxious and agitated, 2=cooperative and tranquil, 3=drowsy but responds to command, 4=asleep but responsive to glabellar tap, 5= asleep, with a sluggish response to tactile stimulation, and 6= asleep, with no response) assessed patients' sedation levels during surgery.

In both groups, HR, SBP, DBP, MAP, and SpO_2 values were recorded every 5 minutes. Reduction of SBP more than 30% in comparison to the initial value, or a MAP lower than 60 mmHg, was considered to be low blood pressure; HR less than 50 beats per minute was assessed as bradycardia. Clinically marked hypotension was initially treated with an IV infusion of 0.9% NaCl solution (250 mL over 5 min). If this treatment were ineffective, an IV bolus of 5 mg ephedrine was given as a second step. Bradycardia was treated with 0.5 mg of IV atropine.

Blood samples were drawn one minute before tourniquet deflation (T2), then 5 (T3) and 30 (T4) minutes after tourniquet deflation. Malondialdehyde, SOD, and catalase levels were also measured. Patients were brought to the recovery room after their operation.