

The effects of sevoflurane and propofol anesthesia on renal sodium-potassium adenosine triphosphatase activity during pneumoperitoneum in rats

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ABSTRACT

الأهداف: تقييم نشاط إنزيم صوديوم - بوتاسيوم أدينوسين ثلاثي الفوسفاتيز، بالإضافة إلى تقييم التأثير الوقائي الذي يمكن أن ينتج من استخدام نوعين من المواد المخدرة أثناء استرواح الصفاق.

الطريقة: أُجريت هذه الدراسة في مستشفى غازي، مركز الأبحاث التجريبية، أنقرة، تركيا وذلك خلال الفترة من يناير إلى يوليو 2009م. شملت الدراسة 24 جردي ذكر من النوع ويستر ألبينو، ويبلغ وزنها ما بين 320-380 غرام، وبعد ذلك قُسمت الحيوانات عشوائياً إلى 4 مجموعات بعد أخذ الإذن من مجلس أخلاقيات أبحاث الحيوانات. لقد قمنا بإدخال أنبوب التنفس لكافة المجموعات، ووضعت المجموعات تحت تخدير الكيتامين، غير أن المجموعة 1 لم تتعرض إلى أي تدخل جراحي بعد ذلك. فيما قمنا بإيصال الضغط البطني للمجموعات 2 و3 و4 التي بلغ عددها 18 حيوان إلى 10 ملي متر زئبقي بواسطة نفخ ثاني أكسيد الكربون لمدة ساعة واحدة. ولم يتم تخدير المجموعة 2 بأي من المواد المخدرة، فيما حُدثت المجموعتين 3 و4 بالبروبوفول وسيفوفلورين. وبعد نهاية التجربة قمنا باسئصال الكلية اليسرى لكافة الحيوانات من غير قتلها، وبعد مرور 24 ساعة قمنا بجمع عينات البول لتقييم مستويات الكرياتينين والبروتينات.

النتائج: لقد كان نشاط إنزيم صوديوم - بوتاسيوم أدينوسين ثلاثي الفوسفاتيز أقل لدى المجموعات 2 ($p=0.014$) و3 ($p=0.019$) و4 ($p=0.032$) مقارنةً بالمجموعة 1، كما كانت درجات التشريح المرضي لدى المجموعات 2 ($p=0.017$) و3 ($p=0.028$) و4 ($p=0.039$) أعلى من الناحية الإحصائية من المجموعة 1. ولم يكن هنالك فرق من الناحية الإحصائية بين المجموعات 2 و3 و4 وذلك فيما يخص نشاط إنزيم صوديوم - بوتاسيوم أدينوسين ثلاثي الفوسفاتيز والتشريح المرضي.

خاتمة: أظهرت الدراسة بأن ارتفاع الضغط البطني مرتبط بتدري وظيفة الكلية وتركيبها، وأثبتت الدراسة بأن المواد المخدرة التي يُزعم دورها في وقاية الكلية ليس لها أي دور في تحسين أو زيادة سوء تدري الوظائف الكلوية المرتبطة باسترواح الصفاق.

Objectives: To evaluate the renal sodium-potassium adenosine triphosphatase (Na⁺/K⁺ATPase) activity, kidney morphology, and the probable protective effects of 2 different anesthetic agents used during pneumoperitoneum (PP).

Methods: The study was performed at Gazi University Experimental Research Center, Ankara, Turkey between January and July 2009. Twenty-four Wistar albino male rats weighing 320-380 g were randomly allocated to 4 groups after receiving ethics committee approval. All rats were cannulated, intubated, and ventilated under ketamine anesthesia. No further surgical intervention was performed for group I. An intraabdominal pressure (IAP) of 10 mm Hg was created by CO₂ insufflation in 18 animals for one hour. The animals in group II received no further anesthetic agents, while the animals in groups III and IV received propofol and sevoflurane. At the end of the protocol, all animals underwent left nephrectomy without sacrificing. Urine was collected from each animal for the following 24 hour for the evaluation of urine creatinine and protein.

Results: The activity of renal Na⁺/K⁺ATPase was significantly lower in groups II ($p=0.014$), III ($p=0.019$), and IV ($p=0.032$) compared to group I. The pathological score was significantly higher in groups II ($p=0.017$), III ($p=0.028$), and IV ($p=0.039$) compared to group I. No statistically significant difference was found among groups II, III, and IV in terms of Na⁺/K⁺ATPase activity and pathological scores.

Conclusion: Elevated IAP is related with impaired kidney functions and morphology, and the so-called renoprotective agents neither improved, nor worsened PP-related renal impairment.

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Pneumoperitoneum (PP) is created during laparoscopic surgery by insufflation of carbon dioxide (CO₂) to the peritoneal cavity, and this causes an increase in intraabdominal pressure (IAP). The elevation of IAP during laparoscopic surgery plays a role in organ failure by decreasing splanchnic and renal blood flow.^{1,2} Studies evaluating the renal effects of PP in the literature suggest not only the decrease in renal blood flow, but also additional factors like the compression of renal parenchyma and renal vein, the increase in renal vascular resistance, and the alterations in neurohormonal responses as contributing factors for renal adverse effects.³ Sodium-potassium adenosine triphosphatase (Na⁺/K⁺ATPase) is an integral membrane protein located at the proximal tubules of the kidney, and is one of the energy providers for the secretion and reabsorption of many solutes.^{4,5} The ischemia induced renal tubular damage results in the impairment of Na⁺/K⁺ATPase activity.⁶ Both volatile and intravenous anesthetics have varying effects on renal blood flow and kidney functions. Propofol, a lipid soluble intravenous anesthetic agent, widely used for induction and maintenance of anesthesia, has shown to attenuate renal ischemia/reperfusion (I/R) injury.^{7,8} Likewise, one MAC sevoflurane also protects against renal I/R injury in animal models.⁹ The aim of this study is to investigate the effects of 2 different anesthetic regimens, propofol based total intravenous anesthesia and sevoflurane based inhalational anesthesia, on renal functions during surgical procedures, which are prone to produce renal dysfunction, such as PP in rats. Sodium-potassium adenosine triphosphatase activity, urine protein, and creatinine levels and histopathological evaluation were used to assess the renal effects of both PP, and 2 different anesthetic regimens during PP in the present study.

Methods. The study protocol was approved by the Gazi University Animal Ethics Committee, Ankara, Turkey and performed according to the guidelines of the Faculty of Medicine, Research Committee of Gazi University between January and July 2009. Twenty-four adult Wistar albino male rats weighing 320-380g were used in the study. Animals were housed in individual metabolic cages in a temperature-controlled environment with alternating 12 hours lights and dark cycles, and fed

with standard diet and tap water ad libitum. All surgical procedures were performed by the same researcher in sterile conditions. After administrating 50 mg/kg intramuscular ketamine (Ketalar, Eczacibasi, Turkey), all animals were intubated with 18G over-the-needle catheter (the inner stylet is shortened by 5 mm in order not to traumatize the oropharynx and trachea), and mechanically ventilated (Harvard Apparatus Inspira ASV Ventilator, Holliston, Massachusetts, USA). After positioning the animals on a heating pad to maintain body temperature at 37°C, a 24G venous catheter was inserted to the tail vein to deliver the drugs. Femoral artery was also cannulated for continuous measurement of blood pressure during the study. Pneumoperitoneum was created by insufflating CO₂ via 18G intravenous cannula inserted into peritoneal cavity up to a pressure of 10 mm Hg by an abdominal CO₂ insufflator.

Twenty-four animals were divided into 4 groups; Control (Group I): The animals were cannulated, intubated, and ventilated as described above, and no additional intervention was performed. Sham (Group II): After cannulation, intubation, and ventilation, PP was performed as described above, and maintained for an hour. Propofol (Group III): The animals were cannulated, intubated, and ventilated. Pneumoperitoneum was performed as described above. Propofol (Propofol 1% Fresenius, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) infusion was started with a rate of 10 mg/kg/hour and PP was maintained for an hour. Sevoflurane (Group IV): The animals were cannulated, intubated, and ventilated. Pneumoperitoneum was performed as described above. Sevoflurane (2%) was started, and PP was maintained for an hour. Femoral arterial cannula was connected to a pressure transducer (Physiogard SM 786, Bruler®, Lower Saxony, Germany) to measure arterial pressure continuously during the procedures. At the end of the procedure, all animals underwent midline laparotomies, and left kidney of each animal was excised. All the kidneys were divided in a horizontal plane into 2 equal pieces for biochemical and pathological evaluation. Half of the kidneys were kept in 10% formaldehyde solution for pathological examination. The other halves were first washed with deionized water to discard blood contamination and were kept at -80°C until the day of biochemical analysis. After the surgery, all animals were kept in metabolic cages for the following 24 hours, and their urine samples were collected for assessment of urinary creatinine and protein levels. They were also maintained on a standard diet and water ad libitum during this period. Also, acetaminophen was added to water with a concentration of 2 mg/mL for postoperative analgesia.

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Biochemical analysis. After the last exposure, kidney tissues were homogenized in a 4 volumes of ice-cold Tris-HCl buffer (50 mmol/l, pH 7.4) using a Heidolph DIAX 900 homogenizer after cutting off the kidney into small pieces with scissors for 2 min at 5000rpm. After performing 60 minutes of centrifuging at 5000g for removing debris, clear upper supernatant fluid was taken. An equal volume of an ethanol/chloroform mixture (5/3, [volume/volume]) was used in order to extract the supernatant solution. The final solution was again centrifuged at 5000g for 30 min, and the clear upper layer was taken and used in the analysis of enzyme activities and protein assays. All preparation procedures were performed at 4°C.

Determination of ATPases activity. ATPase activities were assayed according to the modified method by Tsakiris et al.¹⁰ The reaction mixture for Na⁺/K⁺ATPase assay contained 5.0 mM magnesium chloride, 80.0 mM sodium chloride, 16.0 mM potassium chloride, 50.0 mM Tris-HCl buffer, pH 7.4, in a final volume of 1.00 mL. Disodium salt and vanadium free ATP to final concentration of 3mM was added in order to start the reaction. The addition of one mm ouabain under the same conditions was used for control assays. The medium was incubated at 37°C for 30 minutes then reaction was stopped by adding 10% (w/v) trichloroacetic acid. A control for non-enzymatic decomposition of ATP was performed in parallel. Sodium-potassium adenosine triphosphatase activity was calculated by the difference between 2 assays. Released inorganic phosphate (Pi) was measured using the method of Kyaw et al.¹¹ All samples were run in duplicate. Specific activity of the enzyme is expressed as IU/mg protein. Protein content in samples was determined using the method of Lowry et al¹² with bovine serum albumin as a standard.

Histological evaluation. One half of the harvested kidney was fixed in buffered 10% formaldehyde solution (pH 7.4). Paraffin-embedded sections were prepared and stained with the hematoxylin-eosin. The damage of the proximal convolute tubules was evaluated by a pathologist blinded to the groups. Twenty proximal tubules of superficial and middle cortex were assessed for morphological changes induced by ischemia reperfusion

(I/R) injury, and the following scoring system was used 0=normal histology; 1=slight alteration (loss of brush border, mild hydropic degeneration); 2=mild (intensive hydropic degeneration, mild vacuolization); 3=moderate (shrunken nuclei, intensive vacuolization); 4=severe (necrotic or apoptotic cells, denudation or rupture of basement membranes); and 5=necrosis (total necrosis of the tubule).¹³

Statistical analysis. Data were analyzed using Statistical Package for Social Sciences version 11.0.5 for Windows (SPSS Inc., Chicago, IL, USA). Data were presented as mean values ± standard deviation (SD), and analysis of variance (ANOVA) was used to compare the parametric data, followed by post hoc with the Bonferroni adjustment. Values of $p < 0.05$ were considered to be statistically significant.

Results. No statistically significant difference was observed among all groups in terms of mean arterial pressure. The activity of Na⁺/K⁺ATPase was significantly lower in Groups II, III, and IV when compared to Group I (Group I-Group II [$p=0.014$], Group I-Group III ($p=0.019$), Group I-Group IV [$p=0.032$]). No statistically significant difference was found among Groups II, III, and IV (Figure 1). The

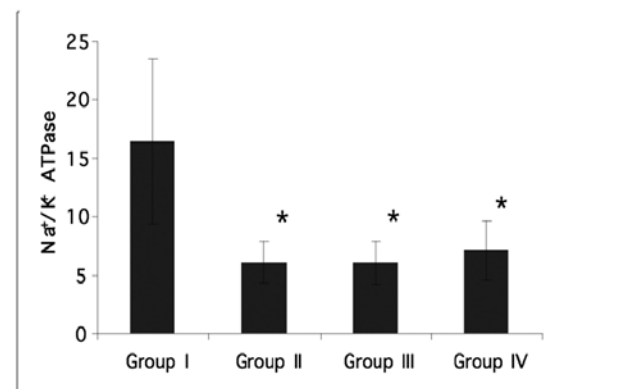


Figure 1 - Sodium-potassium adenosine triphosphatase (Na⁺/K⁺ATPase) values of the groups. *Groups I-II ($p=0.014$), Groups I-III ($p=0.019$), Groups I-IV ($p=0.032$) compared to Group I.

Table 1 - Urine creatinine, urine protein levels, and pathological scores (mean ± standard deviation) of all groups (* $p < 0.05$ when compared to Group I).

Variables	Group I (n=6)	Group II (n=6)	Group III (n=6)	Group IV (n=6)
Urine creatinine (% mg)	24.70 ± 7.41	41.66 ± 12.20*	53.67 ± 25.40*	40.27 ± 13.09*
Urine protein (mg/mL)	0.25 ± 0.09	0.22 ± 0.11	0.24 ± 0.14	0.36 ± 0.19
Pathological score	0.75 ± 0.50	2.20 ± 0.63*	2.00 ± 0.63*	2.00 ± 0.94*

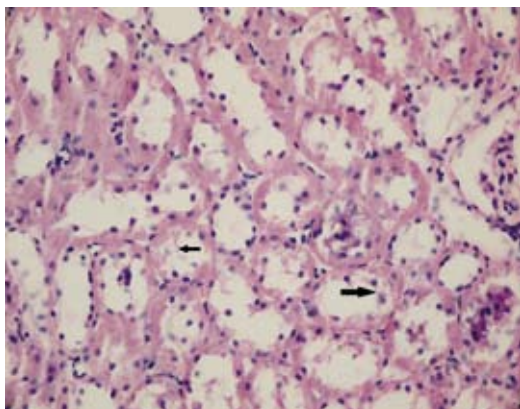


Figure 2 - Slight alteration, loss of brush border, mild hydropic degeneration at the tubular epithelium (arrows) (Hematoxylin and eosin, X400).

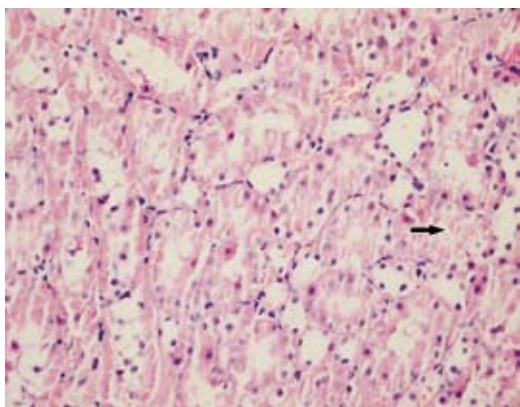


Figure 3 - Mild alteration, intensive hydropic degeneration, mild vacuolization (arrows) (Hematoxylin and eosin, X400).

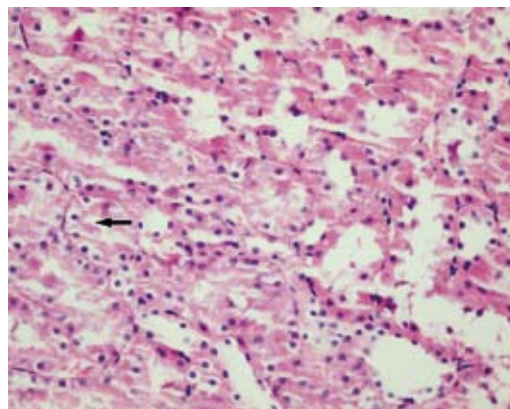


Figure 4 - Moderate alteration, shrunken nuclei, intensive vacuolization (vacuolar degeneration at the tubular epithelium, arrows) (Hematoxylin and eosin, X400).

pathological score was significantly higher in Groups II, III, and IV when compared to Group I (Group I-Group II [$p=0.017$], Group I-Group III [0.028], Group I-Group IV [$p=0.039$]). No statistically significant difference was found among Groups II, III, and IV (Table 1) (Figures 2-4). The urinary creatinine level was significantly higher in Groups II, III, and IV when compared to Group I (Group I-Group II [$p=0.032$], Group I-Group III [$p=0.026$], Group I-Group IV [$p=0.033$]). No statistically significant difference was found among Groups II, III, and IV (Table 1). No statistically significant difference was observed among all groups in terms of the urinary protein levels (Table 1).

Discussion. The effects of elevated IAP on renal functions have been widely evaluated in the literature, and the decrease in renal blood flow, the increase in renal vascular resistance, and the alterations in neurohormonal responses were presented as the causes of renal impairment during PP.³ Although the impairment at the tissue level is unavoidable during

PP, it is not well documented in the literature. The Na⁺/K⁺ ATPase is an appropriate biochemical marker to evaluate the ischemia induced renal damage. In this study, the activity of Na⁺/K⁺ ATPase was found to decrease during PP, and this activity did not recuperate under the administration of either anesthetics.

In a Schafer et al¹ review, 5 different animals were evaluated for the effects of laparoscopy on intraabdominal blood flow. They showed a reduction up to 40% in the renal blood flow during PP. Similarly, Demyttenaere et al¹⁵ reviewed 17 animal studies and presented the relationship among PP, renal perfusion, and kidney function. In 14 of these 17 studies, the authors reported mild to moderate decrease in renal blood flow during PP, and this reduction in the renal blood flow in these animal studies was found to be strictly related to the level of PP. In this study, we applied PP of 10 mm Hg to the groups II, III, and IV. The significant reduction in renal Na⁺/K⁺ ATPase activity in PP groups suggests that this effect could be the result of decrease in the renal blood flow.

Sodium-potassium adenosine triphosphatase is an integral protein located at the basolateral membranes directly interacting with membrane associated cytoskeletal proteins, and is shown to redistribute due to the disruption of the cytoskeleton of proximal renal tubules following an ischemic insult. Coux et al^{4,5} evaluated the effects of ischemic insult alone, and ischemic insult with short-term reperfusion on Na⁺/K⁺ ATPase activity of the kidney. They demonstrated that the ischemic injury lasting longer than 40 minutes results in a decrease in renal Na⁺/K⁺ATPase activity and intracellular ATP levels with renal dysfunction.⁴ In another study, they evaluated the effect of one hour reperfusion following renal ischemia of 40 minutes, and

demonstrated no curative effect of one hour reperfusion on Na⁺/K⁺ATPase activity, and a partial curative effect on ATP with prominent renal dysfunction.⁵ The effects of longer reperfusion times following 40 minutes ischemia were also evaluated by Molinas et al.¹⁶ They showed that after renal reflow of 48 hour, despite normalization of Na⁺/K⁺ATPase activity and ATP levels, the renal dysfunction still proceeded. In this study, we excised the left kidneys after one hour PP and found that one hour PP results in a decrease in renal Na⁺/K⁺ATPase activity, similar to the findings of Coux et al.⁵ For the next 24-hour, we collected urine samples from all rats, and aimed to evaluate the renal functions. Urine creatinine and protein were measured, and significant increases in urine creatinine with unchanged urine protein levels were realized demonstrating the renal dysfunction due to PP. At the end of this period, we could have excised the right sided kidney, and evaluated the effects of long term reperfusion injury following an ischemic insult created by PP on renal Na⁺/K⁺ATPase activity and kidney morphology. We believe that this is the limitation of our study.

Both sevoflurane and propofol are shown to be renoprotective agents. In an animal study by Shiga et al,¹⁷ the effects of bolus injection and continuous infusion of different anesthetics on renal blood flow were evaluated by Doppler ultrasound. Neither route of propofol was found to decrease the cortical blood flow.¹⁷ In a renal I/R study, Yuzer et al⁷ demonstrated that the usage of propofol was protective in terms of functional, biochemical, and morphological damaging of the kidney, and attributed this finding to the antioxidant effect of the drug. Wang et al⁸ demonstrated that propofol treatment has significantly attenuated the renal dysfunction and kidney injury associated to ischemic reperfusion injury in rat kidney. Their data also demonstrated that propofol effectively reduced the increase of blood urea nitrogen and serum creatinine levels, and the mean histological score induced by I/R. Sevoflurane was also shown to reduce the renal damage related to I/R. Lee et al^{9,18} evaluated the effects of sevoflurane on renal I/R with in vitro and in vivo studies, and concluded that sevoflurane activates a cytoprotective signaling cascade especially in renal proximal tubules via transforming growth factor β1 pathway. They moreover demonstrated the protective effects of this volatile agent on renal morphology. In this study, we also evaluated the so-called renoprotective effects of propofol and sevoflurane during PP. We have found that both of the anesthetic agents neither improved, nor worsened the effects of PP on renal Na⁺/K⁺ATPase activity and kidney morphology. The

ineffectiveness of sevoflurane on renal Na⁺/K⁺ATPase activity and morphology during PP can be attributed to its degradation products. The drug itself was shown to be nephrotoxic in rats as it undergoes degradation by CO₂ absorbents to different compounds which further metabolizes in rat hepatic enzyme system.¹⁹ The PP also resulted in moderate morphological damage in the kidney and both propofol, and sevoflurane neither improved nor worsened these effects.

Laparoscopic surgery is replacing open approach in many fields of surgery. As it has important effects on physiological parameters and some organ functions, it is essential for the anesthesiologist to understand these changes and the interactions with the agents used during anesthesiology practice.

In conclusion, as we have foreseen, we have observed that the elevated IAP is related with impaired kidney functions and morphology. We have also found that the so-called renoprotective anesthetic agents, propofol, and sevoflurane, neither improved nor worsened the effects of PP on renal functions. However, the protective effects of 2 anesthetic agents, sevoflurane, and propofol, may differ in patients with renal problems. Therefore, we believe that the effects of PP and anesthetic agents, propofol and sevoflurane that are believed to be protective against renal I/R injury should be further evaluated in both animal models and patients with impaired renal functions.

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