კობა შანავა

პრე და პოსტკონდიციური მოდელის ეფექტურობის განსაზღვრა შექმნილი პნევმოპერიტონეუმის დროს

ნიუ ვიჟენ უნივერსიტეტის გამომცემლობა
თბილისი
2021

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სამეცნიერო ხელმძღვანელი: **ალექსანდრე ცალუღელაშვილი**
მედიცინის მეცნიერებათა დოქტორი, პროფესორი,
მედიცინის მეცნიერებათა აკადემიის აკადემიკოსი

The protective effects of pre- and postconditioning during pneumoperitoneum

Abstract

Objective: There are several reports of ischemic complications in the clinical practice after the laparoscopy using pneumopertioneum. The conditioning has good effects for various ischemic diseases. This experimental study was designed to evaluate the effects of pre- and postconditioning in the transvaginally created pneumoperitoneum.

Methods: Fifty female Wistar rats were included in the preconditioning series ad divided into the following 5 groups: Sham procedure (Sham), conventional pneumoperitoneum (PP), transvaginal pneumoperitoneum (TV), IV: preconditioning for 2.5 minutes in two cycles (Pre 2.5) and preconditioning for 5 minutes (Pre 5).

Malondialdehyde (MDA), reduced glutathione (GSH), sulfhydryl group (SH-) concentrations, superoxide-dismutase (SOD) and myeloperoxidase (MPO) activity and anti-apoptotic pathway marker p-AKT level and inflammatory cytokine TNF-a were measured. Sixty adult female rats were included in the postconditioning series and divided into four equal groups. Pneumoperitoneum was created by CO_2 insufflation under a pressure of 10mmHg. Rats in the first group (sham) were subjected to only sham-operation or gas insufflation. Second group (TV/Pp) was subjected to pneumoperitoneum for 60 min followed by 30 min of desufflation. Third group (Pp-post-5min) was subjected to pneumoperitoneum for 60 min followed by 5 min of desufflation, 5 min of insufflation and again followed by 30 min of desufflation. Forth group (Pp-post-2cycles) was subjected to pneumoperitoneum for 60 min followed by 2.5 min of desufflation and 2.5 min of insufflation repeated in two cycles and then followed by 30 min of desufflation. The rats were sacrificed from the last insufflation after the 30min, 2h, 6h. Blood was collected in each group after the above mentioned times from every animals.

Oxidative stress markers MDA, SOD, GSH and SH levels and inflammatory cytokines TNF-alpha concentration have been determined.

Results: In the Preconditioning series SOD and GSH levels were lower in PP and TV groups comparing to Sham and preconditioning groups. MPO level in PP and TV groups were lower than in the Sham group but in was high in preconditioning groups. In PP and TV groups MDA amount in plasma was higher than in Sham and preconditioning groups. MDA and SH-levels ware almost same in each group. p-AKT level was low in the TV group comparing to preconditioning and sham groups. TNF-a level was higher in TV and preconditioning groups rather than in the sham group.

In the postconditioning series the levels of malondialdehyde (MDA) in the Pp-post-5 group were significantly decreased compared with TT/PP and post-2.5 groups. The levels of reduced glutathione (GSH) in TV/PP group decreased significantly compared with Sham, Post-5 and Post-2.5 groups.

Levels of sulfhydryl groups (SH) increased in Post-5 groups compare with Sham, TV/PP and Post-2.5 groups. In our observations, we found no differences in the activity of

superoxide dismutase (SOD) between the groups. Concentration of TNF-α in case TV/PP was significantly higher than in Sham and postconditioning groups.

Conclusions: According to our results both pre- and postconditioning may reduce the oxidative injury following the pneumoperitoneum.

Keywords: NOTES, pneumoperitoneum, transvaginal, post-conditioning, oxidative stress

პრე - და პოსტკონდიცირების მოდელის ეფექტურობის განსაზღვრა შექმნილი პნევმოპერიტონეუმის დროს

მიზანი: სამედიცინო ლიტერატურაში აღწერილია ლაპაროსკოპულ ქირურგიაში გამოყენებული პნევმოპერიტონეუმის იშემიური გართულებების კლინიკური შემთხვევები. სხვადასხვა იშემიური მექანიზმის მქონე პათოლოგიური პროცესის დროს პრე- და პოსტკონდიცირების მოდელებს აქვთ კარგი პრევენციული ეფექტი. ჩვენი ექსპერიმენტული კვლევის მიზანია პრე და პოსტკონდიცირების მოდელის ეფექტის შეფასება ტრანსვაგინურად შექმნილი პნევმოპერიტონეუმის დროს.

მეთოდები:

პრეკონდიცირების სერიაში ჩართული იყო 50 მდედრობითი სქესის ვირთაგვა, რომლებიც დაყოფილ იქნა 5 ჯგუფად: პლაცებო (Sham), ჩვეულებრივი პნევმოპერიტონეუმი (PP), ტრანსვაგინური პნევმოპერიტონეუმი (TV), პრეკონდიცირება 2,5 წუთის გამნავლობაში, ორ ციკლად (Pre 2.5) პრეკონდიცირება 5 წუთის განმავლობაში (Pre 5).

შესწავლილ იქნა მალონდიალდეჰიდი (MDA), აღდრენილი გლუტათიონი (GSH), სულფჰიდრილის ჯგუფი (SH-), სუპეროქსიდ-დისმუტაზა (SOD) და მიელოპეროქსიდაზა (MPO). ასევე განისაზღვრა ანტიაპოფტოზური მარკერი p-AKT და ანთებითი ციტოკინი TNF-a.

პოსტკონდიცირების სერიაში ჩართული იყო 60 მდედრობითი სქესის, 300±50გ წონის ვირთაგვა, რომლებიც დაყოფილ იქნა 4 ჯგუფად. 10 მმ. ვწყ. სვ. წნევით CO_2-ის ინსუფლაციით შექმნილ იქნა პნევმოპერიტონეუმი. ვირთაგვების პირველ ჯგუფში (პლაცებო) გამოყენებულ იქნა მხოლოდ აირის ინსუფლაცია. მეორე ჯგუფში (TV/Pp) პნევმოპერიტონეუმი გრძელდებოდა 60 წუთი, რასაც მოსდევდა 30 წუთი დესუფლაცია. მესამე ჯგუფში (Pp-post-5min) პნევმოპერიტონეუმი გრძელდებოდა 60 წუთი, რასაც მოსდევდა 5 წუთი დესუფლაცია, 5 წუთით განმეორებითი ინსუფლაცია და 30 წუთი დესუფლაცია. მეოთხე ჯგუფში (Pp-post-2cycles) 60 წუთიან პნევმოპერიტონეუმს მოსდევდა 2.5 წუთი დესუფლაცია, 2.5 წუთი განმეორებითი ინსუფლაცია, რაც მეორდებოდა ორჯერ, დაბოლოს, 30 წუთი დესუფლაცია.

სისხლი აღებულ იქნა ბოლო ინსუფლაციიდან 30 წუთის, 2 და 6 საათის შემდეგ, ყველა ჯგუფის ყველა ცხოველიდან.

განისაზღვრა შემდეგი ოქსიდაციური სტრესის მარკერების დონე: MDA, SOD, GSH, SH და ანთებითი ციტოკინი TNF-α.

შედეგები:

პრეკონდიცირების სერიაში PP და TV ჯგუფებში SOD და GSH კონცენტრაციები ნაკლები იყო პლაცებო და პრეკონდიცირების ჯგუფებთან შედარებით. MPO დონე PP და TV ჯგუფებში ნაკლები იყო პლაცებოს ჯგუფზე, მაგრამ მეტი იყო პრეკონდიცირების ჯგუფებზე. PP და TV ჯგუფებში, პლაზმაში MDA კონცენტრაცია მეტი იყო, პლაცებო და პრეკონდიცირების ჯგუფებთან შედარებით. MDA და SH-დონეები ყველა ჯგუფში თითქმის თანაბარი იყო. p-AKT დონე TV ჯგუფში ნაკლები იყო პრეკონდიცირებისა და პლაცებოს ჯგუფებზე, ხოლო TNF-a დონე ჭარბობდა TV და პრეკონდიცირების ჯგუფებში პლაცებოს ჯგუფთან შედარებით.

პოსტკონდიცირების სერიაში მელონდიალდეჰიდის დონე Pp-post-5 ჯგუფში მნიშვნელოვნად დაბალი იყო TT/PP და post-2.5 ჯგუფებთან შედარებით. აღდგენილი გლუტათიონის დონე TV/PP ჯგუფში დაბალი იყო პლაცებოს, Post-5 და Post-2.5 ჯგუფებთან შედარებით. სულფჰიდრილური ჯგუფის დონე Post-5 ჯგუფში მაღალი იყო პლაცებოს TV/PP და Post-2.5 ჯგუფებთან შედარებით. ჩვენი მონაცემებით, სუპეროქსიდ დისმუტაზას დონე ჯგუფებში არ განსხვავდებოდა, ხოლო TNF-α დონე TV/PP ჯგუფში მნიშვნეოვნად აღემატებოდა პლაცებოსა და პოსტკონდიცირების ჯგუფთა მონაცემებს.

დასკვნა:

პრე- და პოსტკონდიცირების მოდელებს შესაძლებელია გააჩნდეს პნევმოპერიტონეუმით გამოწვეული ოქსიდაციური დაზიანების შემცირების ეფექტი.

Table of Contents

Diagrams, tables and figures used

Abbreviations

GSH – glutathione
IPC – ischemic preconditioning
IPost – postconditioning
IRI – ischemia reperfusion injury
MDA – malondialdehyde
mPTP - mitochondrial permeability transition pore
SH – sulfhydryl group
SOD – superoxide dismutase
TNFα – Tumor necrosis factor α

Let me express my gratitude to Professor Gyorgy Weber (Department of Surgical Research and Techniques, Faculty of Medicine, Pécs, Hungary) for assistance and support.

INTRODUCTION

The history of laparoscopic surgery

We observe the revolutionary shift from open surgery to surgical laparoscopy. The interest to minimal access surgery comes from the ancient era. Hippocrates in 400 BC described the usage of primitive anoscope to examine hemorrhoids. The eruption of Mount Vesuvius buried the Roman cities of Pompeii and Herculaneum under thick layer of ash in 79 BC. Among artifacts discovered under volcanic material three-bladed speculum was found, which is similar to one used today [1].

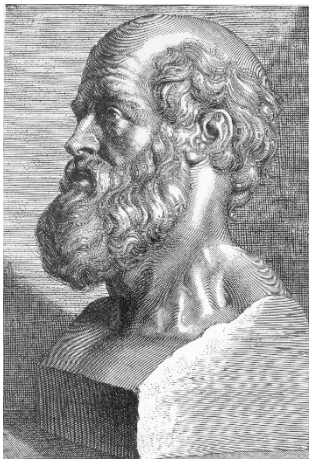


Figure 1. Hippocrates of Kos (460-370 BC)

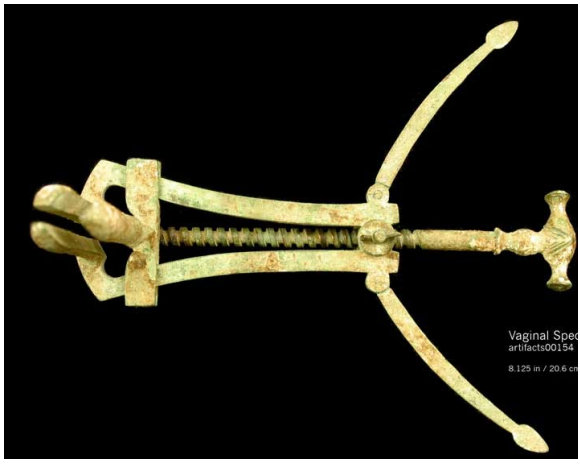


Figure 2. Greek: dioptra Latin: speculum magnum matricis.

Arabian physician Abdulkasim (936-1013) reflected light to direct it through a hollow tube for the examination of cervix in 1012. Avicenna (980–1037) a Persian scholar utilized mirrors to direct sunlight into body cavities for better exploration [2]. Giulio Cesare Arazini (Arantius) (1585) from Bologna reported application of reflected solar rays to peer into nasal cavity. Leonardo da Vinci reported usage of the round flask of water to focus sunlight for exploration of the nasal cavity [3].

Philip Bozzini, a Frenkfurt physitian made the first endoscope with embedded light source in 1805 and named it as a Lichtleiter (light guiding instrument). He examined the urinary tract, rectum and pharynx. Unfortunately, this invention was not appreciated by the medical faculty of the University in Vienna and Bozzini was punished for the clinical application of endoscopy [1].

Pierre Salomon Segalas improved Bozzini's invention and introduced the first clinically applicable cystoscope. It was approved by the Académie de Sciences in Paris in 1826 [4].

At the same time, John Fisher from Boston was using an analogous device for vaginoscopy to evaluate uterine cervix of shy young women.

Antoine Jean Desormeaux from France developed an instrument designed to explore the urinary tract and the bladder in 1853. He named his device "endoscope," and introduced this term for similar instruments. Desormeaux modified the Lichtleiter. He changed the light source from a candle to the flame of alcohol and turpentine mixture which gave much brighter light [6].

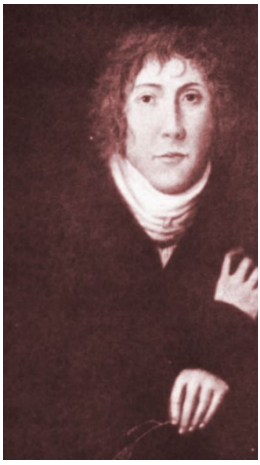


Figure 3. Philip Bozzini

Figure 4. Lichteiter invented by Bozzini.

Figure 5. Endoscope invented by Desormaux.

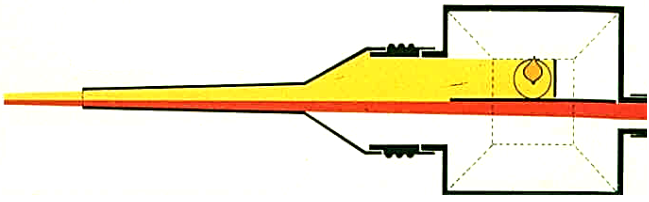


Figure 6. Principle of Lichteiter.

Simultaneously, Francis Cruise from Dublin further improved Desormeaux's Lichteiter by augmenting brightness of illumination with a paraffin lamp. Such endoscope was suitable for rectal, anal, uterine examination as well as for ear, pharynx, and larynx. First clinical application of cystoscope was reported 1869, when Commander Pantaleoni used it for cauterization of bleeding uterine tumor [5].

The first modern-style endoscope with the electric light source at the tip of device was designed by a German physician Maximilian Nitze, and was constructed by instrument maker Joseph Leiter In 1877. The kystoskop had an incandescent platinum or tungsten wire loop for illumination. The wire got very hot and required an ice water-cooling system. The image from larynx, urethra or bladder was reflected through lenses out with magnification [6].

Figure 7. Maximilian Nitze

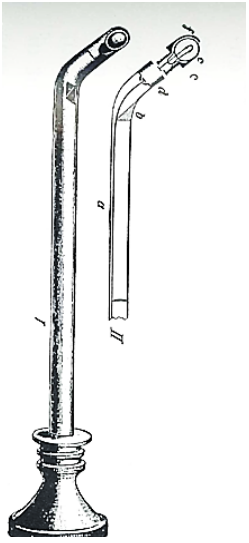


Figure 8. Nitze's cystoscope with cooling system.

In 1887 Nitze improved his cystoscope. He utilized light bulb invented by Thomas Edison. Such device no longer needed a cooling system and was much more simple and convenient. Nitze took first endoscopic photographs.

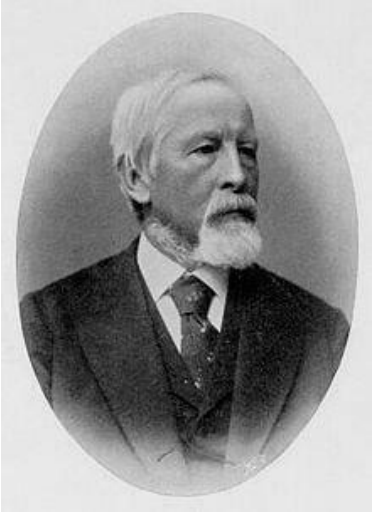


Figure 10. Adolph Kussmaul (1822—1902)

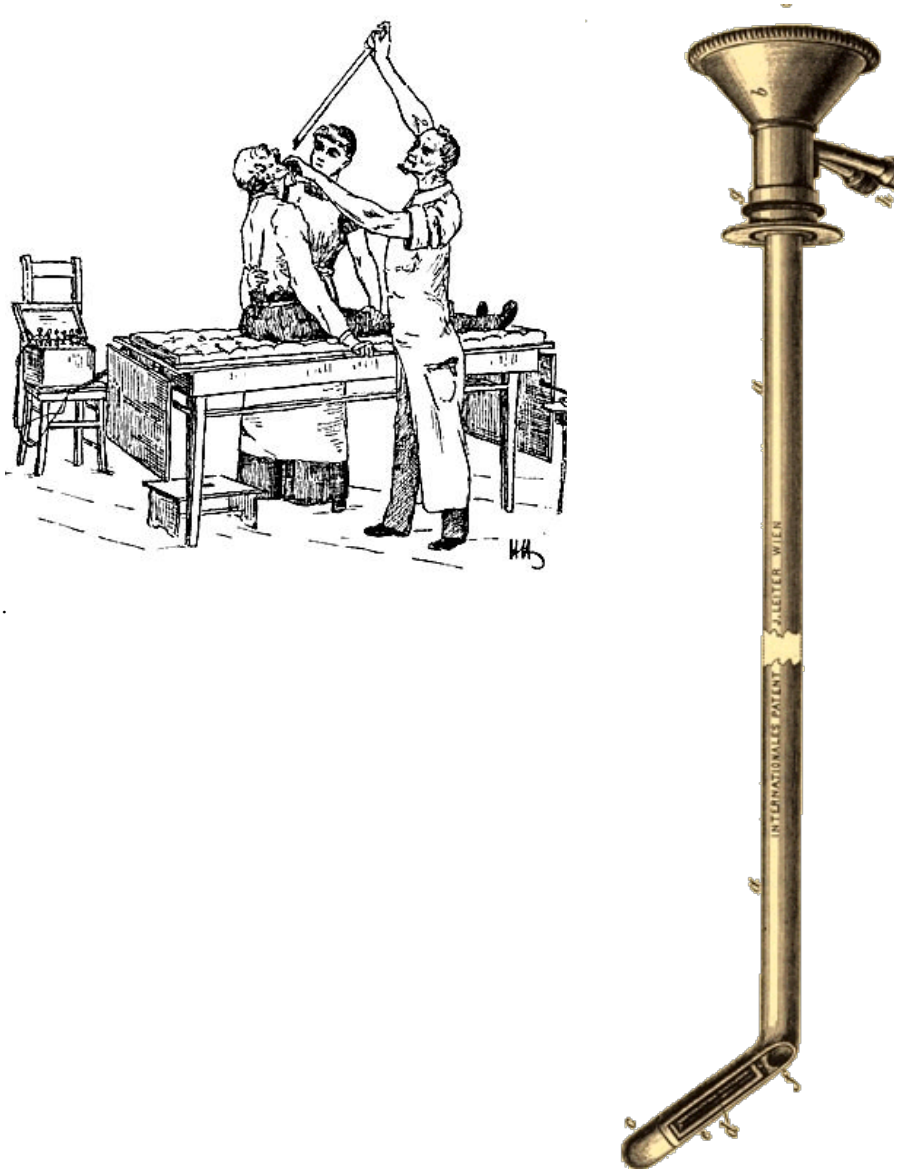


Figure 11. Rigid endoscope invented by Kussmaul

Adolph Kussmaul, German physician was the first person exploring gastric mucosa of a living human. He invented rigid endoscope in 1868 and successfully tested it on sword swallower. He is considered to be the father of endoscopy [7].

Jan Mikulicz-Radecki (1850-1905) Polish-Austrian surgeon reported 183 gastrectomies for gastric cancer. He developed improved models of the esophagoscope and gastroscope in 1881 and used it to discover gastric and esophageal tumors at an early stage. The term trocar was introduced in 1706 and originates from "trocarter troise-quarts", a three-faced perforator enclosed in a metal cannula [8].

Era of laparoscopy begun in early 20th century when Russian gynecologist Dimitri Oscarovic Ott (1855-1929) examined the peritoneal cavity of a pregnant woman by using a head mirror and a speculum introduced into a culdoscopic opening and called this procedure “ventroscopy” [9, 10]. George Kelling, German surgeon made first exploratory laparoscopy in dog model and called it “koelioskopie” [11]. He insufflated abdomen with sterile ear through micro laparotomy and used cystoscope to visualize internal organs. He believed that it is possible to stop internal bleeding from ruptured ectopic pregnancy without laparotomy [12].

Figure 12. Georg Kelling (1866-1945)

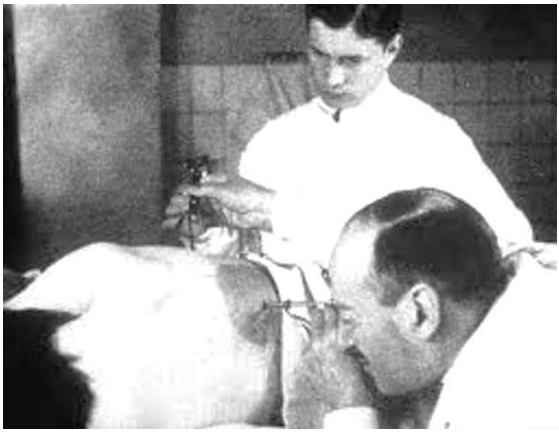


Figure 13. Hans Christian Jacobaeus (1879-1937).

Hans Christian Jacobaeus, from Stockholm, publish his report about laparoscopy performed in the patient with ascites and thoracoscopy in humans in 1911. He introduced the term laparothorakoskopie [13, 14, 15].

The first laparoscopy in the United States was performed in 1911 by Bertram M. Bernkeim (Johns Hopkins University). He utilized a proctoscope with an external light source to explore peritoneal cavity [16, 17, 18].

B. H. Orndoff, An internist from Chicago, reported 42 cases of diagnostic laparoscopy in 1920. He introduced a sharp pyramidal trocar for scope insertion.
In 1924, Zollikofer used CO2 for pneumoperitoneum [19]. In 1929 when Heinz Kalk, from Germany, developed a 135° optics and addition of a working port to laparoscope to undertake some manipulations besides exploration [20].

The first operative laparoscopy was performed in 1933 by the German Fervers. It was an abdominal adhesiolysis under visualization [11].

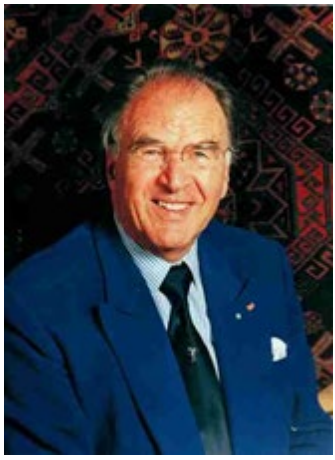


Figure 14. Kurt Karl Stephan Semm (1927 – 2003)

In 1939 he reported about 2000 liver biopsies under local anesthesia without zero mortality [21].

American internist John C. Ruddock introduced forceps with electrocoagulation ability in 1934.

Hungarian Janos Veress developed a blunt-tipped spring-loaded needle in 1938. It was used for save puncture to create a therapeutic pneumothorax for the treatment of tuberculosis. This needle became an essential instrument for safe laparoscopic access [22, 21].

Fourestier, Gladu and Valmiere invented a quartz rod in 1952, to transmit an intense light beam distally along the telescope enabling photographic images [13, 16]. In 1959 image quality was further improved by means of closed circuit television [21].

H. M. Hasson, a gynecologist from Chicago introduced a cut-down technique as more save alternative to a Veress needle in 1971 [23].

In the second half of the twentieth century fiber optic technology experienced an extraordinary progress. Harold H. Hopkins and Narinder Kapany from London and Abraham van Heel from Holland separately published articles about fiber optics in Nature in 1954.

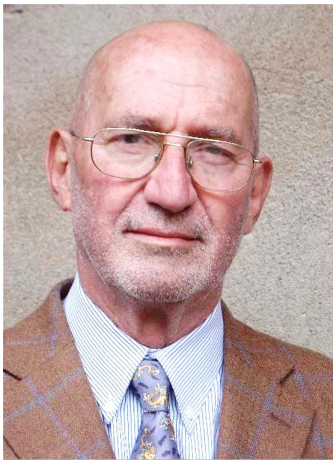


Figure 15. Philippe Mouret (1938-2008)

First prototype developed by Hopkins has an unclear image and was losing light during transmission through glass fibers. Van Heel covered the fiber with a material having a lower refractive index. This technology improved image quality and brightness.

Lawrence Curtiss, an undergraduate at the University of Michigan utilized optical fibers for rigid gastroscope covering them with glass. In 1963 Bergein F. Overholt, developed the first flexible fiberoptic sigmoidoscope-colonoscop.

Kurt Semm from Germany has been called "the father of modern laparoscopy" for his priceless contributions in the field of surgery. He was a pioneer which understood diagnostic and therapeutic capabilities of laparoscopy. He named it “pelviscopy” being a director of the Gynecologic Services of the University of Kiel. He developed specific equipment dedicated for save and convenient laparoscopy: an automated

electronic CO2 insufflator, thermocoagulation device, high-volume irrigation and aspiration device, extra- and intracorporeal endoscopic knotting devices and uterine manipulator. His extraordinary ideas were unacceptable for surgical and gynecological communities. Colleges requested him to undergo a brain scan. Kurt Semm had to undergo a brain scan because they suspected that only a person with brain damage would perform laparoscopic surgery [13, 21, 23].

Semm had performed first ovariectomies, myomectomies, ovarian cysts resections, removals of tubal pregnancy. Medical journals rejected Samm's publications stating laparoscopic technique was "unethical". Despite this skepticism, on September 13, 1980 Semm performed the first laparoscopic appendectomy and presented his experience at a surgical meeting in Germany [24]. After presentation the President of the German Surgical Society wrote a letter to the Board of Directors of the German Gynecological Society requesting suspension of Semm's privileges. Despite such unfriendly attitude he published over 700 articles and presented laparoscopy at 1,300 scientific events in Germany, other European countries and USA.

In 1982 Liver biopsies were the first laparoscopic procedures done by general surgeons [25]. In 1986 Warsaw, Tepper and Shipley used laparoscopy for staging of pancreatic cancer, with accuracy rate of 93% [26].

Philippe Mouret from France performed the first laparoscopic cholecystectomy in Lyon On March 17, 1987 [27, 28]. After gynecologic laparoscopy on a woman suffering with the gallstone disease removed gallbladder without laparotomy. He performed procedure successfully and discharged the patient without complication.

Actually, first laparoscopic cholecystectomy was performed in 1983 by the Russian surgeon Lukichev, but its publication was limited for the Russian literature, and it remained unknown [29, 30].

Laparoscopic cholecystectomy was performed in Boblingen, Germany on September 12, 1985 by Erich Muhe. He performed 94 such procedures before Mouret's first laparoscopic cholecystectomy but German medical society criticized and rejected his innovation [31, 32, 33].

Because of a rapid recovery, less postoperative pain, shorter hospital stay and better cosmetic results laparoscopic cholecystectomy has spread rapidly [34].

In the 1960s diagnostic mediastinoscopy was introduced to evaluate respectability of the lung cancer. Diagnostic thoracoscopy was used by Brad Rodgers and Jim Talbert at the University of Virginia from 1970s to identify lung pathology and perform biopsies.

Patrick C. Steptoe from Bristol, England, used a laparoscopic technique to harvest oocytes and performed first successful in vitro fertilization in the late 1970s. He was awarded a Nobel Prize for this achievement.

A new era in laparoscopy began in 1982 after invention of miniature electronic real-time, high-resolution video camera that could be attached to the endoscope and stream electronic image to the monitor or recording device. Now surgeons were able to stand upright and share high-resolution, magnified intracorporeal image with assistant.

Laparoscopic equipment necessary for quick and safe surgery were developed: clip applicators, staplers, harmonic scalpel, Ligasure, endoscopic ultrasound probes etc.
This made possible safely perform complex surgical procedures as splenectomy, hemicolectomy, hysterectomy, gastrectomy, nephrectomy, proctectomy, surgical arthroscopy, gastric bypass, hepatectomy etc.

Now surgical laparoscopy is a rapidly developing field of surgery with incredible perspectives.

To make laparoscopic surgery further minimally invasive and absolutely scarless new experimental technique has been investigating. Natural orifice transluminal endoscopic surgery (NOTES) is an experimental surgical technique of performing abdominal passing endoscope through a natural orifice (mouth, urethra, anus, etc.) and then through an internal incision in the wall of stomach, vaginal fornix, bladder or colon [35, 36, 37].

The ability to make operations from outside of the abdominal cavity, looking at the operative field on the monitor made possible to develop surgical robots. The history of robotic surgery starts in 1985 when Kwoh performed neurosurgical biopsies with greater precision using a robot Puma 560 [38, 39]. Three years later, transurethral resection of the prostate was done by Davies et al using the Puma 560 [40]. Robots offer accuracy, integration with modern imaging technology, greater range of motion, haptic feedback (force and tactile), natural hand-eye coordination, dexterity, 3-dimensional view [41]. Robotic surgery is in its infancy but it is clear that this is the future of laparoscopy [42].

Complications of Laparoscopic Surgery

Laparoscopic surgery replaces many open operations worldwide. Its main advantage is minimal trauma to the organs and tissues compared to open surgery. This is achieved by small wounds in the abdominal wall resulting less pain, minimal traumatic stress, less wound complications and systemic response to surgery as well as quick recovery, rapid return to normal activities and reduced healthcare cost [43, 44, 45].

Although, alongside complications associated with the open surgery, laparoscopy has specific problems: complications related to the trocar insertion procedure, hemodynamic, metabolic and respiratory consequences of the pneumoperitoneum itself [46], and complications caused by long-lasting Trendelenburgh position of the patient.

Table 1. Classification of laparoscopic surgery complications.

COMPLICATIONS DUE TO PNEUMOPERITONIUM
Gas specific effects
Carbon dioxide (CO2)
Gas embolism
Hypercarbia
Respiratory Acidosis
Cardiac arrhythmia
Post-operative shoulder pain
Nitrous oxide (N2O)
Combustion.
Pressure Specific Effects
Excessive Pressure on IVC
Bradycardia due to vasovagal response
DVT, pulmonary embolism
Respiratory Dysfunction
Effects on renal system
Pneumothorax
Subcutaneous and subfascial emphysema
Air Embolism
SURGICAL COMPLICATIONS
Insertion of primary and secondary trocars
Extra-peritoneal gas insufflation
Mediastinal emphysema
Pneumothorax
Pneumo-omentum
Injury to gastro-intestinal tract
Stomach
Bowel penetration

Bladder injury
Bladder penetration.
Blood vessel injury
Gas embolism
Puncture of liver or spleen
Thermal Instrument related injuries
Thermal necrosis of organs.
Inadvertent organ ligation.
Unrecognized hemorrhage.
Mechanical Instrument related injuries
COMPLICATIONS RELATED TO PATIENT POSITIONING
Cardiovascular
Decreased left ventricular function
Decreased cardiac output
Decreased mean arterial pressure
Increased systemic vascular resistance
Increased central venous pressure
Increased pulmonary artery pressure
Increased pulmonary capillary wedge pressure
Respiratory
Reduced vital capacity
Decreased respiratory plateau pressure
Decreased compliance
Hypoxemia
Central nervous system
Increased intracranial pressure
Decreased cerebral perfusion pressure
OTHER SPECIFIC POSTOPERATIVE COMPLICATIONS
Pelvic inflammatory disease
Omental and Richter's herniation
Port site hernia
Port site metastasis

Carbon dioxide is the commonly used gas to create pneumoperitoneum. It is necessary for the development of working space in the peritoneal cavity. We will discuss here complications associated to the pneumoperitoneum only. Besides hypothermia and postoperative pain associated with the residual gas in the abdominal cavity pneumoperitoneum can initiate clinically significant hemodynamic, metabolic, respiratory effects. High risk patients can develop acute organ failure [47] or lethal complications [48, 49, 50]. Altogether, minimal invasive surgery is maximal invasive from a physiological

point of view and that consequently patients subjected to endoscopy should be carefully selected [47, 48, 49, 50, 51].

Subcutaneous emphysema

The incidence of the subcutaneous emphysema is 0.3–3.0% laparoscopic operations [52, 53, 54] The reason could be a gas escape through tear of parietal peritoneum or parietal pleura to the subcutaneous space or mediastinum or congenital defect in the diaphragm [55, 56, 57].Clinically significant capnothorax or capnomediastinum can complicate subcutaneous emphysema after extra peritoneal inguinal hernia repair [58, 59, 60, 61]. Congenital defect in the diaphragm can be the way of CO2 escape. Capnothorax is suspected when SpO2 drops and mean airway pressure increases. Nicholson et al reported about capnopericardium with carbon dioxide accumulation in the pericardial cavity [62].

Carbon dioxide embolism

CO2 embolism could be caused by accidental puncture of the blood vessel or solid organ. Otherwise, the gas can enter circulation through tear in the wall of the damaged vessel. 68% of asymptomatic patients have some amount of CO2 bubbles in right atrium by transesophageal echocardiography [63]. Although, incidence of the symptomatic embolism is low (0.0014–0.6%) but a mortality rate is about 28% [64]. Symptoms include mill-wheel murmur, arrhythmias, hypotension, cyanosis, asystole.

Main reasons of cardiac arrest during laparoscopic surgery are gas embolism and vasovagal reflex due to quick intraperitoneal insufflation. Its incidence is about 2–20 cases per 100,000 laparoscopic interventions [65].

Respiratory complications

After insufflation, abdomen is distended and the diaphragm is pushed upwards compressing lungs. As a result pulmonary compliance is reduced to 35-35% and total lung volume is significantly decreased [66, 67, 68, 69] leading to hypoxemia. This may result to intrapulmonary shunting and ventilation-perfusion mismatch [70].

CO2 is a very soluble gas which is rapidly absorbed by peritoneal layer and results hypercapnia and acidosis as well as hypoxemia of tissues [71, 72, 73, 74]. Demiroluk et al [75] PaCo2 is significantly high (42 mmHg) during the pneumoperitoneum [76, 77]. These effects are rare in healthy patients but are very Significant in ASA III and IV patients [78]. During pneumoperitoneum excretion of carbon dioxide increases by 7-25% [79, 80, 81, 82]. It depends on alveolar and mixed venous CO exchange rates, which are themselves functions of cardiac output, alveolar ventilation and respiratory quotient [83].

Cardiovascular complications

Arrhythmias take place in 14–27% of laparoscopic operations [64]. Sinus tachycardia and ventricular extrasystoles usually are caused by release of catecholamines and rarely are dangerous. Much more hazardous are bradycardia, nodal rhythm, atrioventricular

dissociation and asystole which generally are caused by the vagal nerve mediated cardiovascular response following acute stretching of the peritoneum [64].

Intraabdominal pressure more than 20 mmHg causes the compression of the inferior vena cava, decreases cardiac refill and results hypotension. It happens in 13% of laparoscopic surgery cases and is dangerous [84].

Moderate to severe hypercarbia affects cardiac function. Main reasons are acidosis caused by hypercarbia leading to sympathoadrenal stimulation and decreased cardiac preload caused by increased intra-abdominal pressure [85]. PaCO2

Above 45–50 mmHg has a direct vasodilatary effect and acts as a myocardial depressant. The cardiac index decreases by 30% during laparoscopic cholecystectomy as demonstrated by Westerban et al [86]. Dexter et al [19] compared cardiovascular effects pneumoperitoneum of 7 mmHg and 15 mmHg pressure. Strike volume depression was significant in the 15 mmHg group [87]. Joris et al [22] showed that 15 mmHg pneumoperitoneum causes elevation of the mean arterial pressure by 35%, systemic vascular resistance by 65%, pulmonary vascular resistance by 90%, and cardiac index decreases by 20% [88]. Pneumoperitoneum causes oliguria [89, 90, 91] The mechanism is associated with direct decreased renal blood flow [92], which results activation of the renin-angiotensin-aldosterone system leading to cortical vasoconstriction in kidneys. As proven by Nguyen et al ADH, renin, and aldosterone levels are evidently increased during laparoscopy [93].

Oxidative stress and reperfusion injury

Oxidative stress is defined as a disturbance between the prooxidant and the antioxidant balance resulting in cell injury by oxidation of proteins, lipids and DNA [8].

After ischemia, only the restoration of blood flow can prevent irreversible tissue necrosis and loss of organ function [94]. But restoration of oxygenated blood flow can increase the degree and size of injury in excess of that was caused by the ischemia alone [95, 96]. This phenomenon is called an **ischemia-reperfusion injury (IRI)** [95].

Mitochondria as a primary place of oxidative phosphorylation ATP synthesis is vulnerable for IRI. ATP deficiency affects the function of the nonspecific mitochondrial permeability transition pore (mPTP) located in the inner mitochondrial membrane. mPTP is closed in normal physiologic state as well as during ischemia, but opens after myocardial reperfusion, due to mitochondrial Ca^{++} overload, oxidative stress and rapid normalization of pH [97]. Only molecule smaller than 1.5 kDA can pass this pore [98] they cause mitochondrial swelling [97] and rupture of the outer membrane, release of enzyme cytochrome c, a potent activator of the apoptotic pathways, into the cytoplasm [99, 100], activation of proteolytic enzymes and death by [101, 102, 103]. The inhibition of mPTP opening participates in the mechanism of IPC, pharmacological preconditioning and IPost [104, 105, 106, 107]. mPTP consists 3 components: voltage-dependent anion channel (VDAC), adenine nucleotide translocator (ANT) and cyclophilin-D (CYP-D) [108, 109].

The exposure of a single organ to ischemia and reperfusion may result in inflammatory reaction in distant non-ischemic organs, subsequently leading to multiple organ failure [110, 111]. This process is initiated by toxic ROS transported by blood flow to distant tissues where activated neutrophils release cytokines and vasoactive substances including nitric oxide [112, 113].

Ischemia and reperfusion happens during clinical emergencies (myocardial infarction, intestinal or limb ischemia, cerebral stroke) as well as in during surgical interventions as in organ transplantations, operations when tourniquet is used like Pringl's maneuver or endarterectomy [114].

Splanchnic ischemia caused by pneumoperitoneum leads to free radical production [115]. After deflation and restoring splanchnic perfusion, oxidative stress from the ischemic injury remains [116] causing the ischemia-reperfusion injury that occurs as a result of a pneumoperitoneum [115, 117, 118, 119]. Standard laparoscopic procedures are done with low pressure (7 mm Hg), standard pressure (12 mm Hg) or high pressure (15 mm Hg) Pneumoperitoneum.

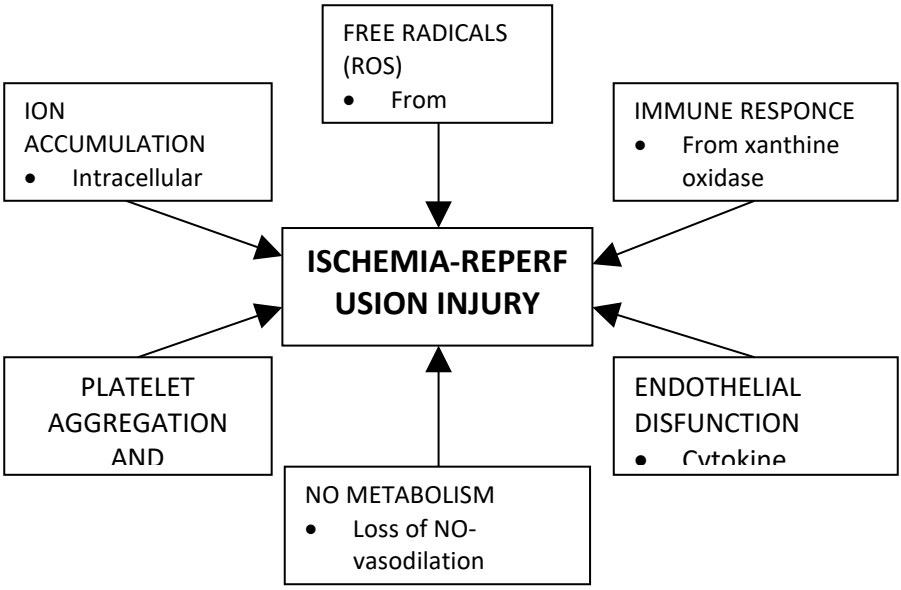


Figure 16. Effects of IRI.

Ischemia-reperfusion injury caused by pneumoperitoneum has been studying on animals [148, 129, 120] and humans [121, 122]. Reactive oxygen products: superoxide and hydroxyl radicals released during reperfusion cause reperfusion injury: DNA damage, lipid peroxidation, and mitochondrial membrane and cell damage [123, 124, 147]. Reactive

oxygen products are main substances responsible in the pathogenesis of cellular damage associated with ischemia-reperfusion injury [125]

Antioxidative system regulates the activity of reactive oxygen products. Those antioxidants are plasma enzymes: catalase, superoxide dismutase and glutathione peroxide [126, 127]. Pneumoperitoneum facilitates formation of free radicals which induce lipid peroxidation and as a result, reduction of the antioxidants' effectiveness [128, 129] This imbalance between the oxidative and antioxidative systems is defined as oxidative stress [130].

It is evidenced that oxidative stress can be reversed by several agents. Erythropoietin administration before pneumoperitoneum decreases LDH, TNF-α, and MDA levels [131], melatonin zinc, pentoxifylline, and NAC administration before pneumoperitoneum insufflation and deinsufflation decreased kidney MDA level [132, 133].

Dexmedetomidine, which is used for sedation, anxiolysis, and analgesia in the intensive care unit demonstrated protective effect against ischemia-reperfusion injury of the kidney [134]. It reverses the oxidative stress caused by pneumoperitoneum. It is clinically proved that besides local protective effect on kidneys, Dexmedetomidine has systemic anti-inflammatory effect decreasing cytokines [134, 135].

This imbalance can be estimated by measurement of total oxidant status (TOS) and consumed antioxidant status [130].

Propofol, the one of the frequently used anesthetic medications has antioxidant properties and can scavenge free radicals, reducing the oxidative stress [136]

Significant but temporary increase of serum creatinine was reported by Krisch et al during 10 mmHg pneumoperitoneum in rats [137].Comparing laparoscopic cases done with pneumoperitoneum and wall lifting technique Miki et al [138] demonstrated a decrease in glomerular filtration rate and urine output during pneumoperitoneum only.

Pneumoperitoneum leads to decreased blood flow in intraabdominal organs [139, 140]. If intra-abdominal pressure is greater than normal physiological portal pressure (7–10 mm Hg) splanchnic ischemia occurs [141]. Knolmayer et al [142] reported decrease in gastric ph. Liver transaminase elevate [143] and Kupffer cell function affected [144]. Elevation of intraabdominal pressure from 10 to 15 mmHg decreases stomach blood flow by 40–54%, small gut blood flow by 32%, liver by 39% [145].

Clinical studies showed that a pneumoperitoneum during laparoscopic surgery decreases intestinal perfusion and microcirculation [146, 147].
Hypoperfusion of intra-abdominal organs [148, 149, 150, 151, 152] leads to ischemia and the oxidative stress response.

Oxygen is essential for cellular life [36]. The energy released by reduction of oxygen to water in the mitochondria enables synthesis of the adenosine 5'-triphosphate (ATP) and phosphocreatinine, maintaining cellular membrane potentials [94].

Reactive oxygen species (ROS) are natural by-products of this process. They are ions, with unpaired electrons which appropriates high chemical reactivity [153]. ROS are able to interact with proteins, lipids, DNA causing oxidative damage which is called

oxidative damage [154, 155]. Most important ROS is the superoxide anion radical ($O2^-$) [153]. Mitochondrial enzyme xanthine oxidase also generates ROS [154]. High amount of ROS can be lethal to the cells [36].

Deprivation of oxygen inevitably leads cell teeth but it needs some time for changes to get unreversible. 4 hours for muscle to 4 days for bone [156]. The biochemical result of ischemia is reduced oxidative phosphorylation and ATP production. The deficiency of ATP leads to failure of the ATP-dependent ionic pump, accumulation of intracellular sodium, hydrogen, and calcium ions resulting in a decrease in pH causing cellular swelling and acidosis [94, 95]. This process in the capillary endothelium results increased permeability of vascular wall and tissue swelling [157, 158].

Endotheliocytes are sensitive to oxygen deprivation and ischemia leading to weaken barrier function of the vessel wall, fluid leakage and increased permeability [159, 160]. In case of prolonged ischemia cell death is inevitable. Reperfusion is able to significantly worsen tissue damage. Reperfusion exacerbate injury caused by ischemia [161]. Morphological features of cell damage is less after 4 hours of ischemia then 3 hours of ischemia followed by 1 hour [162].

Initiated as a local process, substances formed by inflammation enter bloodstream and exhibit systemic effects affecting distant organs. Substances like oxidase-derived toxic ROS launch inflammation causing chemotaxis and sequestration of leucocytes [163].

Activated neutrophil res release nitric oxide which is vasoactive mediator of inflammation [164, 165].

Acidosis has protective effect during initial stages of ischemia. Reperfusion leads to rapid restoration of the intracellular pH which could have paradoxical toxic effect t [166]. Inhibition of the oxidative phosphorylation in mitochondria during ischemia results to decreased ATP generation. Mitochondrial permeability transition pore (mPTP) which is located in the inner membrane of the mitochondria is usually closed during normal conditions and during ischemia. Reperfusion opens because of the high Ca++ concentration and quick restoration of pH [167].

Being nonspecific pore, open mPTP allows molecules lesser then kDA move freely across the membrane. Proteins can not cross the membrane keeping osmotic pressure gradient and mitochondria become distended [168]. Swelling results damage of the outer membranes and activation of apoptosis via release of cytochrome c enzyme [169, 170]. Protons freely moving through inner membrane uncouple oxidative phosphorylation which is the main function of mitochondria and destructs ATP molecules via hydrolysis. ATP dependent mechanisms of homeostasis maintenance fail and irreversible necrotic cell death will result [171, 172, 173].

Myocardial infarction and ischemia-reperfusion injury

The incidence of acute myocardial infarction is increasing worldwide [174].

First report about ischemia-reperfusion injury was made by Jennings et al. 1960 ligating coronary vessels on canine heart. They concluded that reperfusion accelerate the development of necrosis.

Modern treatment using endovascular restoration of obstructed coronary blood flow is the pathogenic and very effective treatment. However, reperfusion results paradoxical cardiac dysfunction, so-cold "no-reflow" phenomenon. Clinically it exhibits cardiac arrhythmias and myocardial stunning, which could be lethal [175, 176, 177].

1. No-reflow is the state when after releasing occlusion of the artery coronary circulation is still obstructed because of microvascular damage or clogging.
2. Myocardial stunning is the condition when myocardial dysfunction still exists despite successfully restoration of the coronary flow without myocardial necrosis [178].
3. Microvascular obstruction is the "inability to reperfuse a previously ischemic region"[179]. The mechanism of this phenomenon is the impaired vasodilatation, external capillary lumen obstruction by external compression by swelling cardiomyocyte, microembolization from atherosclerotic plaques, neutrophil and platelet plugging, release of the vasoactive and thrombogenic mediators [180, 181, 182, 183]. Coronarography shows slow coronary blood flow, typical flow velocity profile and blush grade [184]. 30-40% of patients with normal flow in recanalized coronary artery angiogram myocardial contrast echocardiography demonstrates microvascular obstruction [185]. Similar results are shown with contrast-enhanced cardiac MRI [186, 187] and myocardial perfusion nuclear scanning [188].
4. Lethal myocardial reperfusion injury is the reperfusion-induced death of cardiomyocytes that were viable at the end of the ischemia [189]. It is suggested that reperfusion injury is good target for cardioprotection during PPCI because as shown on experimental models and clinical observations of MI therapeutic intervention during early stages of myocardial reperfusion can reduce the size of necrosis by 40-50% [190]

These potentially dangerous phenomena could last for several weeks after endovascular treatment [175, 191]. Severe reperfusion injury could result to death of myocardial cells which were viable before restoration of the coronary blood flow [154].
The size of necrosis is larger after longer ischemia and expanding from deeper to superficial areas of the myocardium [192]. It is demonstrated on both experimental myocardial infarction model and in patients with ST-segment elevation myocardial infarctions that therapeutic interventions at the beginning of myocardial reperfusion reduced the size of the MI size by 40%–50% [190].

The mechanisms of the reperfusion injury are the similar as in other organs: quick normalization of pH, oxidative stress, Ca++ overload of mitochondrias, chemotaxis of neutrophils and inflammation initiation, release of the proteolytic enzymes and ROS [193]. ROS causes further myocardial damage including stunning syndrome but its role in the lethal reperfusion injury is unclear [194, 195, 196, 197].

There is no consensus about the role of the reperfusion injury in the lethal outcome after successful restoration of the coronary flow. Some scientists consider that reperfusion enhance damage caused by ischemia [198]. Others suggest that reperfusion results additional injury and prognosis depends on the severity of this damage [199]. Moreover, after reperfusion inflammatory mediators like ROS and xanthine oxidase are released. They together with the stimulated leucocytes activate endothelial cells in tissues far from ischemia zone [200] causing microvascular damage and development of the multiple organ dysfunction syndrome [201]. Released inflammatory mediators attract circulating neutrophils resulting there adhesion molecule expression and leukocyte endothelial cell interaction [202, 203]. Preexisting conditions: diabetes, dislipidemia and hypotension aggravate systemic response to ischemia-reperfusion [204].

Ischemia and reperfusion injury of the skeletal muscle

Vascular obstruction and compartment / crash syndrome are main reasons of the acute skeletal muscle ischemia. At initial stages of ischemia metabolism pattern is changed to maintain energy during oxygen deprivation. Oxidation of free fatty acids and aerobic conversion of the ADP to ATP which occurs in normal conditions, discontinues during ischemia [205] and ATP is used mainly for maintenance of the membrane potential and ion distribution. Metabolism is switched to anaerobic pathways which are well developed in skeletal muscle [206].

1. Creatine phosphate which is stored in the muscle donates a phosphate to synthesize ADP which is converted to ATP.
2. Large stores of glycogen in muscle are broken down to synthesize ATP. The byproduct of this process is pyruvate which is converted to lactate freeing the hydrogen ion and causing acidosis. Low pH discontinues glycolysis.

After 3 hours creatine phosphate stores are totally spent and glycolysis only is unable to generate sufficient ATP [207]. After 6 hours necrosis of the muscle develops [208]. After reperfusion cells with irreversible changes could not survive but in case of transitional degree of damage allows restoration of the normal metabolism. However, reperfusion could extend size of necrosis extending cellular damage [209].

After revascularization, local vasodilation develops, which results reactive hyperemia and swelling of the muscle. Longer ischemia leads to less reactive hyperemia [210]. This process is not related to compensatory mechanisms of the oxygen supply but fail of the regulatory mechanisms because of the ischemia [211]. Besides, endothelial edema and leukocyte plugging decrease local blood flow despite hyperemia.

Edema can cause leg or arm compartment syndrome and secondary ischemia because of the obstructed blood flow. Prophylactic or therapeutic fasciotomy is employed to avoid or treat this complication [212].

Ischemia-reperfusion injury damages tissues not only in ischemic area but affects remote tissues and organs resulting development of the multiple organ dysfunction syndrome (MODS) [213] which is diagnosed after ischemia-reperfusion of organs [214] and

after removal of the tourniquet from extremities in both human observations and animal experiments [215, 216, 217].

Ischemia-reperfusion injury of the liver

Liver ischemia-reperfusion injury could be a critical complication of the emergency event or hepatic transplantation procedure which increases likelihood of the lethal outcome [218]. It is associated with the primary non-function of the transplanted liver and postoperative liver failure [219] Liver demands grate amount of oxygen and therefore is very sensitive to ischemia [220, 221]

There are two types of liver ischemia-reperfusion injury: cold and warm ischemia. Cold ischemia is associated with the graft storage before transplantation [222]. Warm ischemia is linked to the temporary discontinuation of the blood supply to the organ because of shock, toxic liver injury, sinusoidal obstruction, Budd-Chiary syndrome or surgical procedure on liver [223, 224].

Besides universal mechanisms, hepatic ischemia-reperfusion injury is linked to cell mediated hepatocyte damage because of activation of Kupper cells which are resident liver macrophages [225]. Modifying metabolic pattern during hypoxia they generate large amount of ROS [226]. After reperfusion they get activated via Toll-like receptor 4 (TLR4) and TLR4 complement system. As a result they release a lot of pro-inflammatory cytokines: tumor necrosis factor (TNF) and interleukin- 1 (IL-1) aggravating hepatic ischemia reperfusion injury [227].

Complex mechanism of hepatic IRI could be good target for pharmacological interventions to prevent or reduce the damage. Methylprednisolone, ulinastatin, glucose, trimetazidine [228, 229, 230], nilotinib, a receptor tyrosine kinase inhibitor [231]. Ischemic injury activates pro-survival genes which mediate protection against oxidative stress [232, 233]. They are controlled by Nrf2 protein. Oxidative stress activates Nrf2 which regulates expression of genes in nucleus [234].

Reduced glutathione (GSH) prevents ischemia-reperfusion injury by scavenging the ROS produced by Kupffer cells [235].

Infusion of N-acetylcysteine before or during the ischemia-reperfusion injury lowers the amount of ROS maintaining glutathione level [236].

N-acetylcysteine has also recently been used in phase IV clinical trials [237, 238] which revealed that it can reduce the expression of biochemical markers caused by partial hepatectomy.

Catalase and superoxide dismutase (SOD) are antioxidant enzymes are effective in the prevention of ischemia reperfusion injury [239].

Heat shock proteins (stress response proteins), are produce in response to stress. Heat shock protein HSP32 (heme oxygenase-1) [240]. HSP70 is also Nrf-2- regulated protein with significant protective effects on liver [241].

The inhalation of volatile anesthetics isoflurane [242] and sevoflurane can decrease ischemia-reperfusion injury of the liver. Sevoflurane can significantly decrease level of transaminase after ischemia-reperfusion of the liver and improve outcome [243].

As mentioned above, increased permeability of the mitochondrial membrane is one of the main mechanisms of the cell damage [244]. Mitochondrial Permeability (MPT) Inhibitors effectively reduce ischemia- reperfusion injury of the liver and reduce ROS generation [245]. Melatonin [246] or edaravone [247] reduce swelling and keep the mitochondrial respiratory chain. Edaravone is effective in cold and warm ischemia in large mammals [248, 249].

Nitric Oxide NO is ae important component of the IRI mechanism. Exogenous delivery of NO could be beneficial against liver IRI. Unfortunately NO is very unstable molecule. Thus, the combination of NO with another another molecule is used for delivery, such as S-nitrosothiols, diazeniumdiolates, and liver-selective NO donors [250, 251, 252, 253].

Green tea extract [254], decrease inflammation during ischemia-reperfusion injury and serve as an antioxidant but clinical usage of this and other herbal medicines need high concentrations and need long pretreatment [255].

Ischemia-reperfusion injury of kidney

Clinical presentation of IRI of the kidney is the acute kidney injury (AKI) [256] which is characterized by high mortality because of the rapid kidney dysfunction [257, 258].

Following pharmacological interventions are used to reduce organ damage. Ascorbic acid bounds free radical [259]. Leptin increases nitrite level [260] and decreases TNF-α concentration. Doxycycline lowers the amount of pro-inflammatory cytokines [261, 262]. Antioxidant levosimendan reduces NO [263]. Iloprost attenuates peroxidation of lipids [264].

Preconditioning of the kidney by small has the ability to be preconditioned by short ischemia, increases resistance to subsequent ischemia-induced injury [265], reduces cell damage and improves the function of ischemic organ 266. The effect could be mediated via diminution of adhesion molecules and inflammatory response [267, 268]. Besides, ischemic preconditioning activates A1 adenosine receptors [269, 270, 271].

Preconditioning and postconditioning for prevention from reperfusion injury

A number of methods are investigated to reduce harm effects of the ischemia-reperfusion injury and several approaches are used clinically [272]. There are Surgical and nonsurgical methods. Pringle Maneuver, total hepatic vascular exclusion and segmental occlusion of the hepatic artery or portal vein are used in modern hepatic surgery to reduce blood loss could get the reason of the parenchymal damage [273].

Usage of intermittent occlusion instead of continuous one can prevent development of IRI [274].

Total hepatic vascular exclusion is results longer operative time, longer post-operative hospital stay as compared to Pringle maneuver [275, 276]. Harmful effects could be reduced by using hypothermic perfusion with cytoprotective solutions and cooling of the organ surface [277]. Local hypothermia decreases oxidative stress and inflammatory answer [278, 279]

Murry and Reimer (1986) determined that cyclic short episodes of ischemia followed by a prolonged ischemia and reperfusion resulted in a significantly decreased infarction extent [280].

Ischemic Preconditioning (IPC), the process by which short bursts of ischemia protects tissues during further sustained ischemic periods. Murry and co-workers in 1986 described IPC, first by as an effective endogenous protective phenomenon [280]. They found the one or more brief episodes of sub-lethal myocardial ischemia and reperfusion increased the resistance of the myocardium to a subsequent sustained ischemic insult. IPC has a bimodal duration of protection. The early (or classic) window of protection lasting up to 3h and a second window of protection (SWOP) - later period of protection lasting between 12 and 72h post preconditioning [281, 282, 283].

Zhao et al (2004) reported that repetitive ischemia applied during early reperfusion, i.e., postconditioning (IPost), is cardio-protective by attenuating reperfusion injury [284]. They stated that Ipost is as effective as IPC in preventing cell damage.
Both phenomena have been extensively studied worldwide but actual mechanism of protection is yet unclear.

Liver ischemia reperfusion injury (IRI) is a main cause of post-operative liver failure, increasing morbidity and mortality following hepatectomy and transplantation [285].

Translation of these experimental data to clinical practice was first attempted by Clavian [286, 287], for hepatectomies.

A meta-analysis did not find any benefit of IPC in liver resections [288] however a meta-analysis of IPC done on transplant donor livers prior to graft retrieval found reduction in recipient mortality and graft loss [289]

There are several mechanism of IPC found: humoral (adenosine, L arginine, eNOS, iNOS, bradykinin, opioid, HIF-1α, SDF1α), systemic (macrophages, pro-inflammatory cytokines, T regs, monocytes) and neuronal.

During ischemia ATP is rapidly decomposes releasing adenosine [290]. This nucleotide binds to receptors A1R, A2AR, A2BR, and A3R [291] and has protective properties against IRI. R75231 affects adenosine utilization decreases liver IRI significantly and increases survival [292]. Administration of the seaminase which disintegrate adenosineaborts effect of the ischemic preconditioning [293]. Adenosine increases of NO release from endothelium of vessels and results vasodilation [294].

Peralta et al. demonstrated in rats that during ischemic preconditioning continuous ischemia for 10–15 min stimulus leads to release of adenosine enough for protective effect but insufficient release of other toxic metabolites [295]. Similarly5 min

ischemic preconditioning was not enough [296] but 10 min ischemia prior to donor organ harvest resulted lower level of postoperative transaminases and less liver injury [297]. Similar results were found for hepaterctomy [298] Mice with genetic lack ofadenisine A1 receptors are more vulnerable for IRI [299]. 8-Cyclopentyl-1, 3-dpropylxanthine (DPCPX) which selectively blocks A1 receptors increase postischemic injury [299]. These data evidence important role of adenosine in IRI mechanism. A2A receptor agonist γ-glutamylcysteine synthase (GCS) decreases IRI, apoptosis degree and lowers transaminases on rat isolated liver immediately prior to reperfusion [300].Nitric oxide (NO), is synthesized from l-arginine by Nitric Oxide Synthase (NOS) [301]. It is an effective vasodilator, having a protective effect during hepatic IR injury [302]. Its vasodilatory property is mediated by inhibition of endothelin synthesis which is an effective vasoconstrictor [303]. NO has hepatoprotective properties again st IRI. Transgenic mice without eNOS are more vulnerable [304,https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5532577/ - B67-jcm-06-00069 305,https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5532577/ - B68-jcm-06-00069 306, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5532577/ - B69-jcm-06-00069 307, 308] but overexpression of eNOS results less IRI in mice [309] Intracellular enzymes - protein kinase C (PKC) are signal transducers from adenosine receptors [310, 311].

Pharmacological suppression of PKC reduces IR injury [312, 313, 314]. PKC inhibitor chelerythrine stops the protective effect of hypoxic preconditioning in an isolated hepatocyte model [315]. An anti-oxidant biliverdin and carbon monoxide are released during the degradation of heme which is catalyzed by enzyme heme-oxygenase (HO-1) [316]. Carbon monoxide is a signaling agent with vasodilatory effects. HO-1 expression is increased in hepatic IRI [317] and protects against hepatocyte apoptosis

Administration of gadolinium chloride in mice upregulates HO-1 expression of Kupffer cells have protective effect. Genetic absence of HO-1 reduce liver injury [318]. Blockage of HO-1 with isoproterenol decreases cytokine release from macrophages [319]. Components of the immune system participate in the response of the IRI. CD4+ T lymphocytes play a key role in IR injury and are rapidly concentrated in the focus of the IRI. Mice lacking CD4+ T lymphocytes, are protected from IRI [320] in the murine liver, kidney [321], and in the murine lung [322]. There are pro inflammatory and anti-inflammatory T cells CD4+ T cells. IPC reduces Kupffer cell activation After IRI [323] decrease ROS and TNFα release resulting less IRI [324] IRI is linked with pro-inflammatory cytokines. TNFα is a main pro inflammatory cytokine that has been shown to play a role in hepatic IRI. Other cytokines: L-2, IL-6, IL-17 are associated with enhanced hepatocyte apoptosis and neutrophil infiltration after IRI [325, 326, 327]. The preventive effect of ischemic pre- and post-conditioning could be mediated via attenuation of the oxidative stress, induction of the the antioxidant enzyme superoxide dismutase, the activation of p38 pro-survival protein, release of antioxidant proteins, activation of PI3K/Akt pro-survival pathway increased cell proliferation [328, 329, 330]. Several methods are investigated to attenuate effects of the pre- and post-conditioning by pharmacological intervention [331]: the adenovirus 2A receptor agonist [332] and atrial natriuretic peptide [333].

Biomarkers of oxidative stress

The intensity of oxidative stress can be measured by quantifying the total oxidant status (TOS) and total antioxidant status (TAS) [334, 335]. Pneumoperitoneum caused oxidative stress in children increased plasma oxidant status and OSI level and decreased total antioxidant status [128]. In order to avaluate the oxidative stress different lipid peroxidation markers are used: nitric oxide, lipid peroxidation, protein carbonyl, and protein sulfhydryl, endogen antioxidant, thiobarbituric acid reactive substances (TBARS) [336, 125].

Activated neutrophils release big amount of reactive oxygen species and proinflammatory cytokines like TNF-α and IL-1β [337, 338, 339, 340]. Leukocytes migrated by chemotaxis release further ROS [340]. The ROS interacts with membrane lipids which increases membrane permeability, resulting cell death [341, 342, 343]. MDA is main biomarker of lipid peroxidation and indicates amount of the cellular oxidative injury. SOD is an enzyme that catalyzes conversion of superoxide radical into hydrogen peroxide.

Proinflammatory cytokines, TNF-α and IL-1β, also participate in muscle cell injury induced by ischemia-reperfusion [344]. IL-1β induces endothelial cells to release IL-8 which contributes to excessive inflammatory responses and up-regulates endothelial cell adhesion molecules [345]. On the other hand, polyclonal antibodies against TNF-α and IL-1, or there receptor antagonists, have protective effect against IR-induced limb injury decreasing neutrophil chemotaxis [346].

Malondialdehyde

During ischemia and reperfusion, ROS leads to oxidative damage, main component of which is the lipid peroxidation. Lipid peroxidation is the oxidation of polyunsaturated fatty acids and destruction of biological membranes and release of toxic metabolites such as malondialdehyde (MDA) [347]. MDA is an indicator of the degree of lipid peroxidation [348, 349, 350].

MDA is produced during the peroxidation of polyunsaturated fatty acids. It interacts with lysine residues generates lysine–lysine cross-links [351] which impair the interaction between oxidized low density lipoprotein and macrophages and thereby to promote atherosclerosis [352].

MDA from plasma samples are detected by a colorimetric assay based on the reaction between MDA and thiobarbituric acid but ELISA kits are also commercially available. This method has better specificity [353].

GSH

S-Glutathionylation is a process of disulphide bridge formation between a cysteine residue and the cellular tripeptide glutathione. This oxidative modification affects protein tertiary structure [354, 355]. As a result its function is modifies which affects following membrane proteins: endothelial nitric oxide synthase [356], ryanodine receptor [357], SERCA [358] and Na+/K+ pump [359, 360]. The consequences of this process could be alterations in

intracellular Na^+ and Ca^{2+} handling, and other key signaling pathways vital for heart function [359, 361].

S-glutathionylation of hemoglobin is being used as a marker of oxidative stress [362]. It is elevated during renal failure, diabetes and hyperlipidemia [363, 364]. Measurement of S-glutathionylation of target proteins is a biomarker for cardiovascular pathological processes and could be used as an instrument with predictive value for prognosis.

S-glutathionylation of proteins is usually measured using a Western Blotting [365]. ELISA with monoclonal anti-glutathione antibody is much sensitivity and specificity [366, 367].

Sulfhydryl (SH) groups

Sulfhydryl (SH) groups (thiols) are considered the potent antioxidants in plasma [368]. Particularly thiol groups present on protein are considered as major plasma antioxidants in vivo and most of the SH-groups are present on albumin molecules and are distributed throughout the body fluids [369, 370].

Superoxide Dismutase (SOD)

SOD is one of the most studied antioxidant enzymes. It facilitates converting the superoxide radical to oxygen and is consumed by oxidative stress [371].

$$2O_2^{\bullet -} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$$

In humans, SOD exists in three forms and functions in various locations throughout the body:

SOD1 or CuZnSOD – intracellular SOD, requires copper (Cu) and zinc (Zn) to perform its function and protects the cell's cytoplasm, the substances enclosed by the cell's membrane where most of the cellular activity occurs.

SOD2 or MnSOD – intracellular SOD, requires manganese (Mn) to perform its function and protects the cell's mitochondria.

SOD3 or EC-SOD– extracellular SOD, also requires copper and zinc and acts outside the cells. [372, 373]

Ascorbic acid and dehydroascorbic acid

Ascorbic acid its oxidized form dehydroascorbic acid remove aqueous phase oxygen free radicals transferring electron transfer and serve as hydrophilic antioxidants [374]. They are unstable and therefore difficult to measure [375].

Inflammatory biomarkers

Small protein molecules - cytokines participate in the responses of the organism to infection, trauma or ischemia. Presently 18 cytokines are known so called interleukins and tumor necrosis factor (TNF). Some cytokines support inflammation and are pro-

inflammatory cytokines, others suppress pro-inflammatory cytokines and are anti-inflammatory cytokines [376].

Cytokines are peptides that are been released during the ischemia and inflammation. There are about 18 cytokines which promote inflammation (pro-inflammatory cytokines), are suppress the activity of the pro-inflammatory cytokines (anti-inflammatory cytokines) [377]. Pro-inflammatory cytokines used as a biomarker are TNF-α, IL-1β, IL-6 and YKL-40. Following anti-inflammatory cytokines are used for the same purpose IL-10, IL-1 receptor antagonist (IL-1Ra) and soluble TNF receptors (sTNF-R) I and –II as anti-inflammatory biomarkers. This classification is too simplistic and a given cytokine may behave as a pro- as well as an anti-inflammatory cytokine [378]. IL-6 has both pro-inflammatory and anti-inflammatory properties, but is a potent inducer of the acute–phase protein response [379].

THE ACTUALITY OF THE RESEARCH AND THE SCIENTIFIC NOVELTY

Gas insufflation of the abdominal cavity is widely employed in modern operative theatre. Pneumoperitoneum is necessary to make workspace. It facilitated tissue dissection entering between planes.

According medical literature pneumoperitoneum can cause many local or systemic dangerous effects. Compression of the visceral and parietal vessels and immobilization of the diaphragm, release of the oxygen radicals, inflammatory mediators and cytokines affecting distant organs - heart, liver, kidneys, bowel, muscles etc. These effects could complicate surgical procedure and could have serious consequences including fatal outcome in critically ill patient.

PURPOSE

The purpose of our study was to determine effective measures for the prevention of harmful effects of the pneumoperitoneum, decrease potential complications and improve outcomes of the laparoscopic surgery.

OBJECTIVES OF THE STUDY

We studied pre- and postconditioning as a simple and effective preventive measure for dangerous effects of the pneumoperitoneum. Effectiveness of these maneuvers needs objective measurement. It is necessary to determine best duration and timing for the procedure to get best results. Therefore, we used rat model of the pneumoperitoneum and monitoring intensity of the harmful consequences of the pneumoperitoneum by measurement of the oxidative stress markers.

ORIGINAL RESEARCH

1. Effects of preconditioning on tissue ischemic injury

Materials and Methods

Animals

We used 50 adult female Wistar rats. Average weight was 300±50 g.

Study groups

In order to determinate effects of the different pneumoperitoneum regimens we divided animals into 5 groups: Group I (Sham) – control group, underwent Sham operation. Group II (PP) transumbilical pneumoperitoneum for 60 minutes. Group III (TV) underwent transvaginal pneumoperitoneum for 60 minute. Group IV (Pre 2.5) preconditioning for 2.5 minutes – inflation for 2.5 minutes, deflation for 2.5, inflation for 2.5 minutes, deflation for 2.5 minutes and transvaginal pneumoperitoneum for 60 minutes, Group V (Pre 5) - preconditioning for 5 minutes – inflation for 5 minutes, deflation for 5 minutes and transvaginal pneumoperitoneum for 60 minutes, (Table I).

I	Sham	Sham operation
II	PP	Conventional pneumoperitoneum for 60 minutes
III	TV	Transvaginal pneumoperitoneum for 60 minutes
IV	Pre 2.5	Preconditioning for 2.5 minutes in two cycles and transvaginal pneumoperitoneum for 60 minutes
V	Pre 5	Preconditioning for 5 minutes and transvaginal pneumoperitoneum for 60 minutes

Table 2. Animal groups of the preconditioning series

Study design

After 24 hours fasting, anesthesia was achieved by the intraperitoneal injection of 37.5 mg/kg ketamine and 3.75 mg/kg diazepam mixture.

Pneumoperitoneum was established by transumbilical or transvaginal insertion of the Veres needle. 10mmHg capnoperitoneum was maintained by automatic insufflator (Karl Storz GmbH&Co. KG, Tuttlingen, Germany).

Biochemical assays

Blood samples from animal harts and tissue samples from kidney were taken for biochemical analysis at thirty minutes after the procedure. Western-blot analysis was used for the estimation of the oxidative stress. The lipid peroxidation markers were measured malondialdehyde (MDA), endogenous antioxidant reduced glutathione (GSH), sulfhydryl-group (SH-) concentrations, superoxide-dismutase (SOD) and myeloperoxidase (MPO)

activity. The inflammatory cytokine TNF-a and anti-apoptotic pathway marker p-AKT level were measured also.

Detection of malondialdehyde (MDA) concentration

A mixture of 4.5 ml thiobarbituric acid (TBA) and trichloroacetic acid (TCA) was added to 0.5 ml diluted blood or plasma. Sample was incubated in boiling water for 20 minutes at 100 °C, cooled in icy water and was centrifuged for 15 minutes at 4000 rpm in the cooled centrifuge blood. MDA concentration was calculated in nM/ml using spectrophotometer at 532 nm. [380].

Detection of reduced glutathione (GSH) and sulfhydryl-group (SH-) concentration

4 ml trichloroacetic acid (TCA) was mixed with 1 ml quintuple diluted blood and was centrifuged at 400 rpm for 15 minutes. Two ml of supernatant was added to 4 ml TRIS puffer (0.4 M, pH: 8.7) and immediately before measurement with spectrophotometer (412 nm) 100 µl 5.5'ditio-bis-2-nitro-benzoe acid (DTNB) was added [381].

Detection of superoxide-dismutase (SOD) activity

One ml of sample blood was mixed with EDTA and 9 ml Hartman's solution and centrifuged for 5 minutes at 2000 rpm. Supernatant was discarder and residue was washed again. One ml of haemolysatum was mixed with 1 ml chloroform and ethanol (2:1) and centrifuged for 4 minutes at 17000 rpm. Adrenalin (16.488 mg adrenalin diluted in 10 ml 0.1N hydrochloric acid) was added to the supernatant and concentration was measured at 480 nm by spectrophotometer. Concentration was calculated in U/ml [382].

Detection of myeloperoxidase (MPO) activity

The 200 ul plasma was added to the 1 ml of the mixture of 10.9 ml Na-citrate and 100 ul o-Dianisidinand was incubated at 37 °C for 5 minutes. After adding 1 ml of the 35% perchloric acid mixture was centrifuged for 10 minutes at 2500 rpm. Spectrophotometer at 560 nm was used to measure MPO concentration which was calculated in U/ml.

Detection of p-AKT concentration

Western-blot using anti p-AKT antibody was used to detect p-AKT concentration in rat kidney tissue (Phospho-Akt, Pan Specific Affinity Purified Pab, Rabbit IgG, R&D Systems, Minneapolis, USA). Detection of density was performed with ImageJ 1.42.

Detection of TNF-a concentration

ELISA kit (Quantikine ® Rat TNF-a/TNFSF1A Immunoassay, R&D Systems, Minneapolis, USA) was used for the detection of TNF-a in the heparinized plasma. Concentration was calculated in pg/ml.

Statistical analysis

SPSS 18.0 (SPSS, Chicago, IL, USA) was used for the statistical analyses with the nonparametric Mann–Whitney U test. Values of p less than 0.05 were considered significant. The graphic expression of the data was performed in box plots.

Results

Neither complications nor technical failures occurred during the experiment. Insignificant vaginal haemorrhage was observed in two cases.

GSH was lower in TV and PP group (TV: 839.37 nM/ml; PP: 785.23 nM/ml) comparing to control (1118.12 nM/ml). In Pre 2.5 and Pre 5 groups GSH was notably elevated comparing with TV and PP groups, (1033.08 nM/ml and 1054.78 nM/ml). This result could indicate effective reduction of the oxidative stress with preconditioning (Fig. 1).

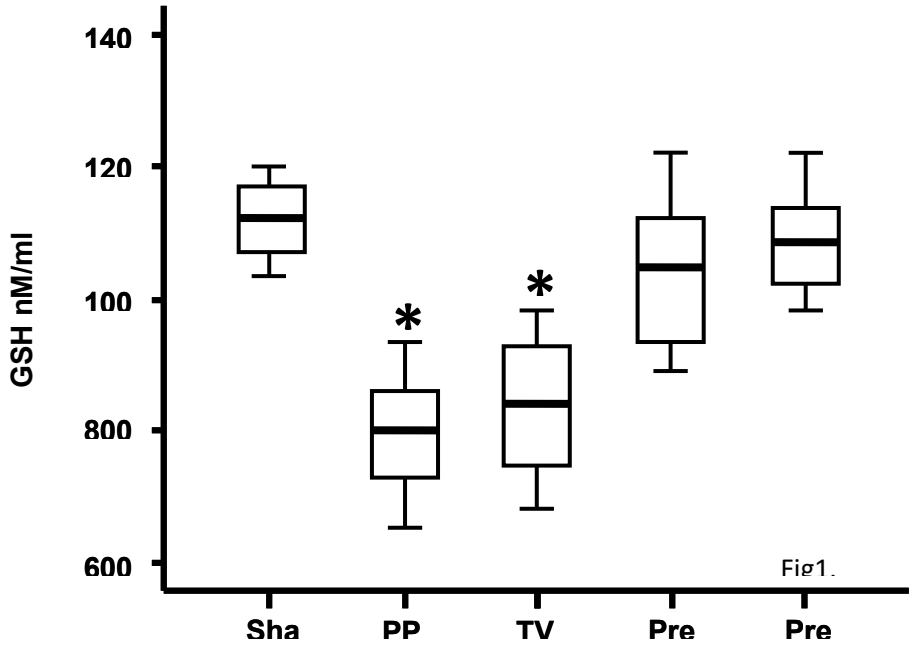


Diagram 1. GSH (reduced glutathione) mean concentration ± SEM

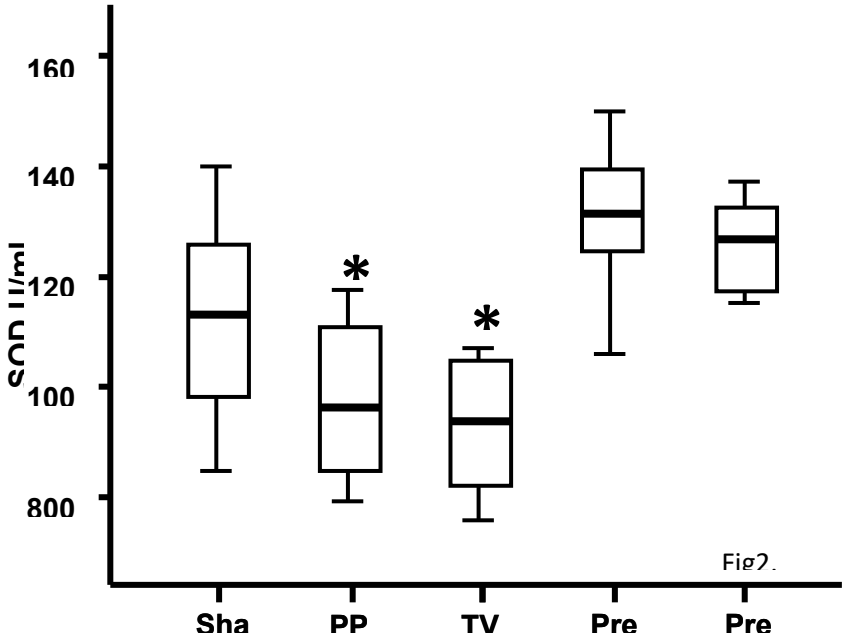


Diagram 2. SOD (superoxide-dismutase) mean activity ± SEM.

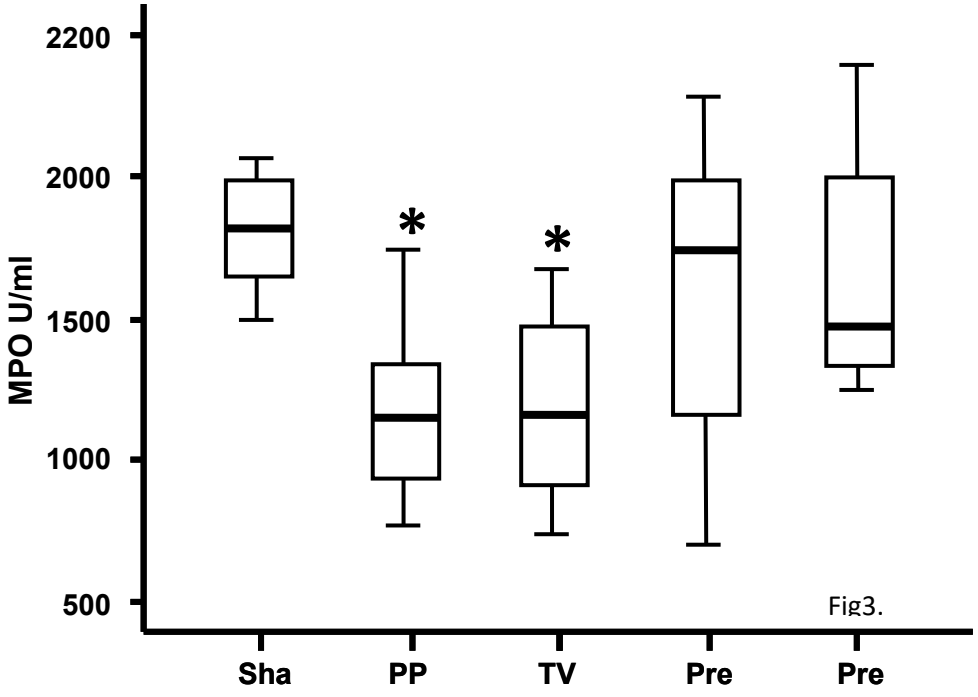


Diagram 3. MPO (myeloperoxidase) mean activity±SEM

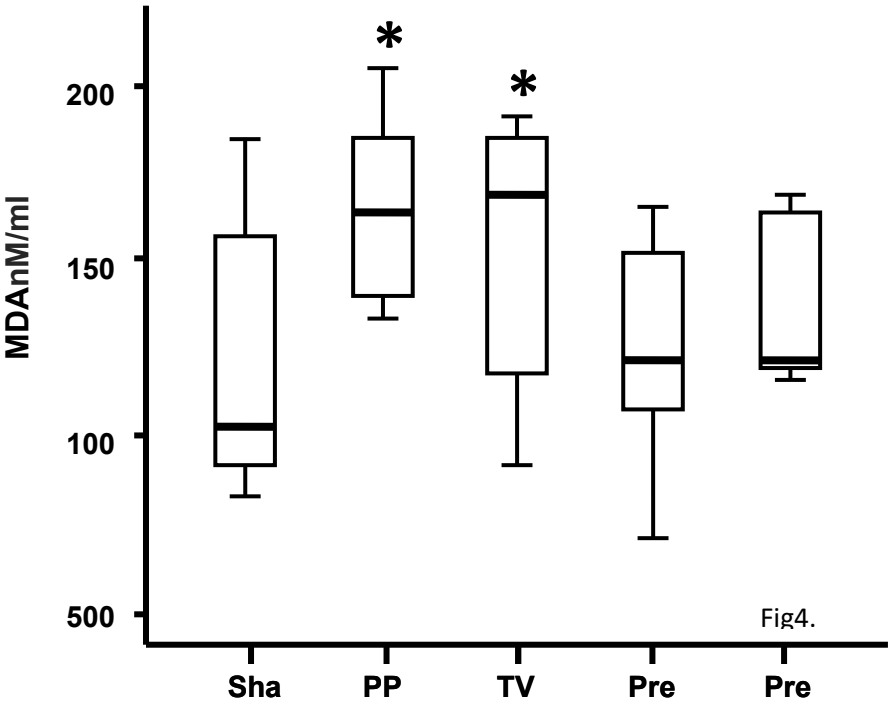


Diagram 4. Plasma MDA (malondialdehyde) concentration ± SEM

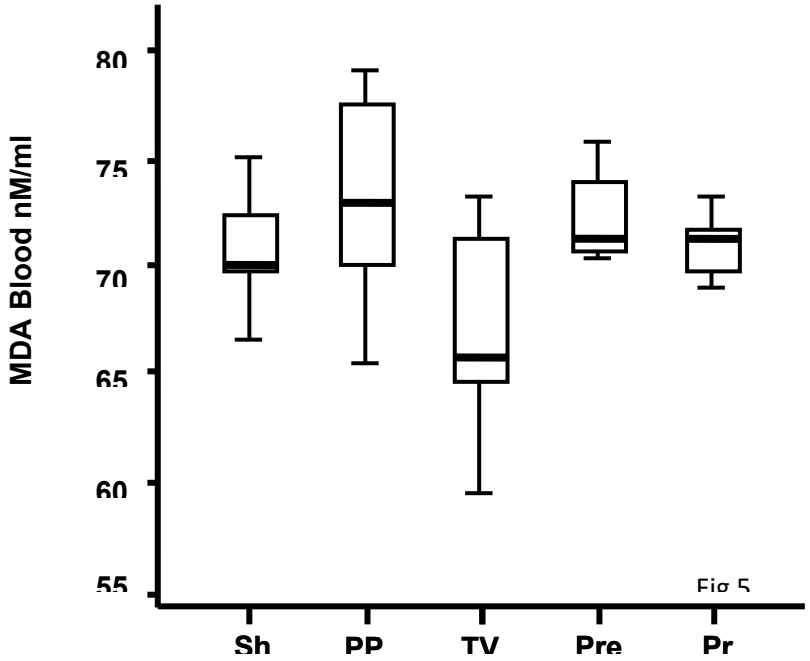


Diagram 5. Blood MDA (malondialdehyde) mean concentration ± SEM.

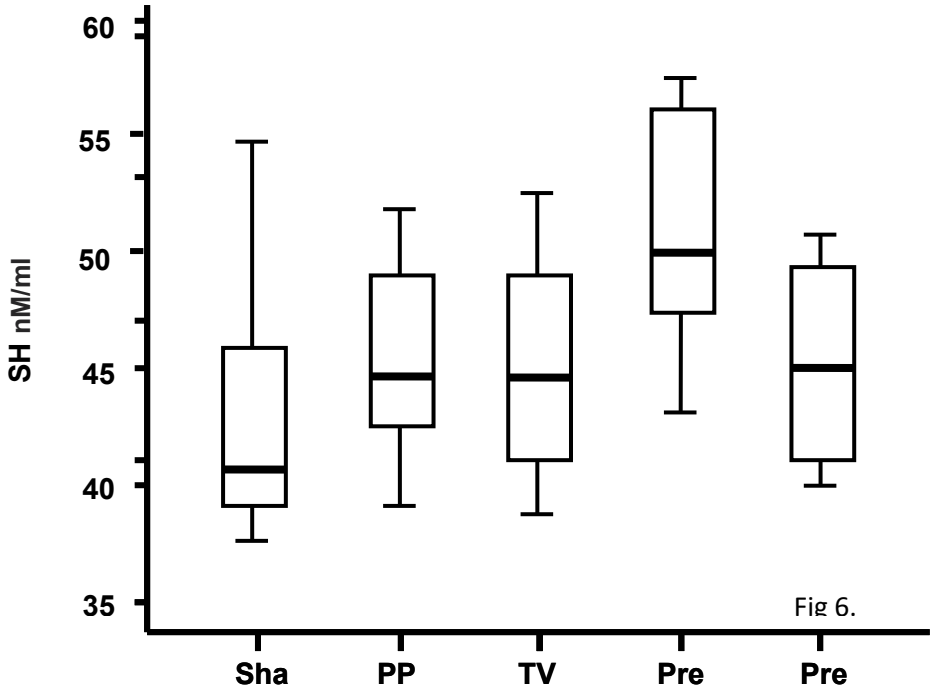


Fig 6.

Diagram 6. Blood SH- (sulfhydryl-group) mean concentration ± SEM.

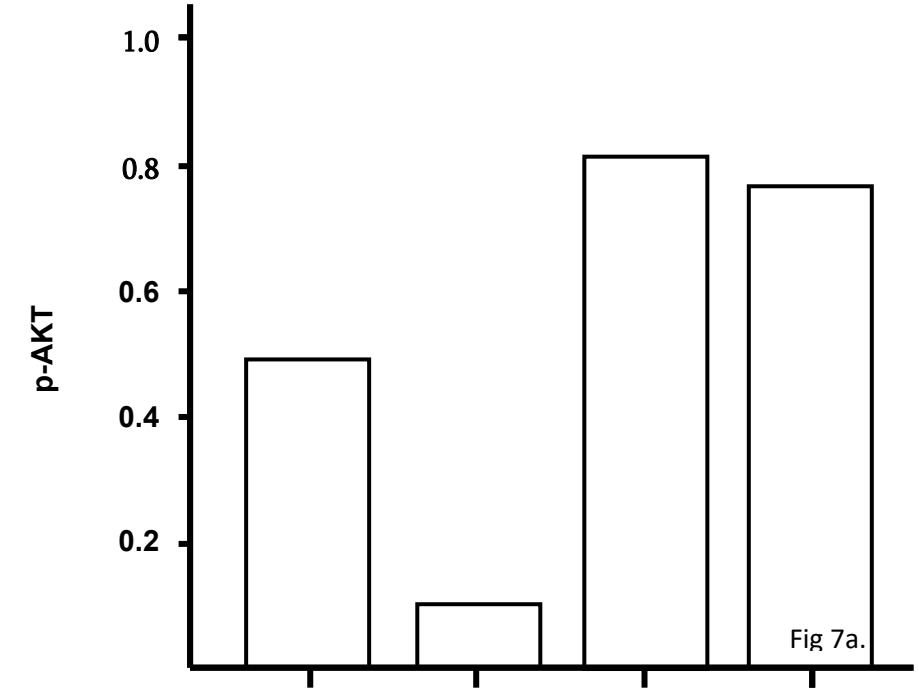


Fig 7a.

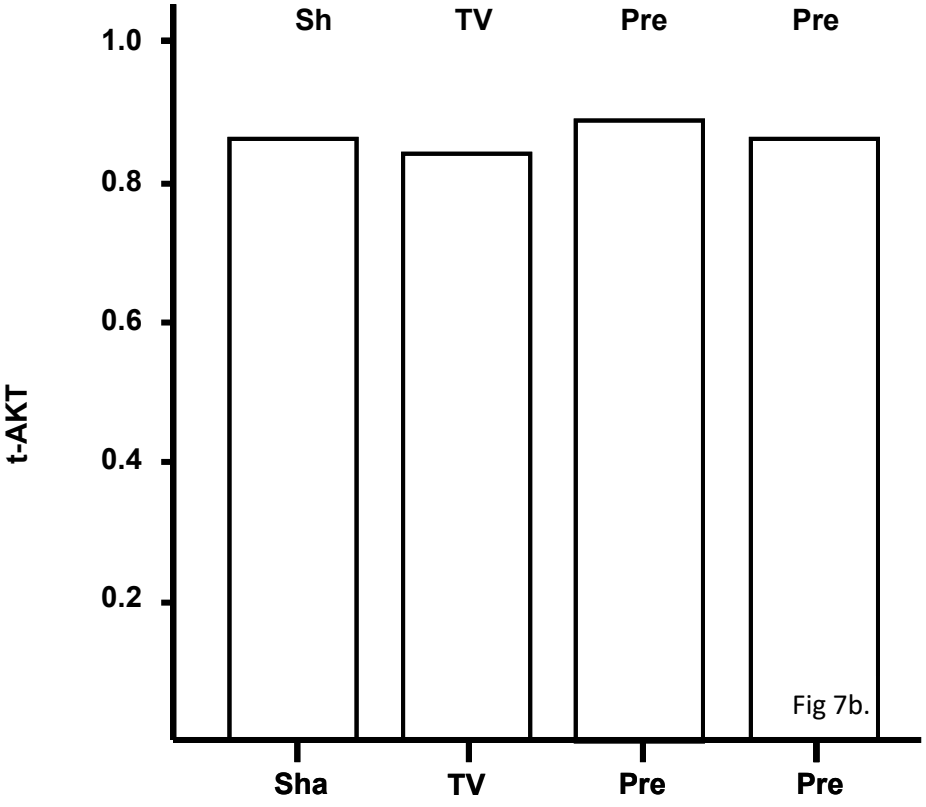


Fig 7b.

Diagram 7. Results of western blots and density level for p-AKT and t-AKT.

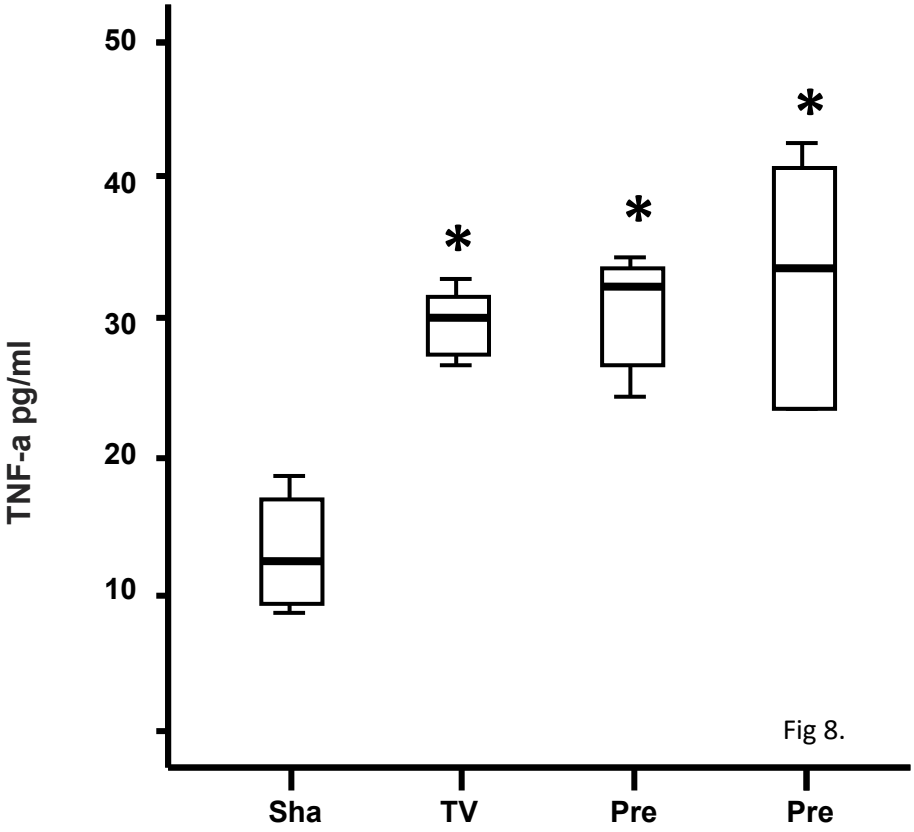


Diagram 8. TNF-a (tumor necrosis factor alpha) mean concentration±SEM.

Comparing to Sham group (1162.58 U/ml), SOD activity was decreased in TV (872.65 U/ml) and PP groups (978.15 U/ml). Pre 2.5 and Pre 5 group results were 2.5: 1372.49 U/ml 1299.76 U/ml correspondingly). According SOD results preconditioning reduced oxidative stress (Diagram 2).

MPO activity was high in preconditioning groups (Pre 2.5: 1.706 U/ml; Pre 5: 1.65 U/ml) but was decreased in TV (1.140 U/ml) and PP (1.223 U/ml) groups comparing to the Sham group (1.717 U/ml). Preconditioning had a favorable effect on MPO activity (Diagram 3).

Adverse effect of the pneumoperitoneum was demonstrated by significantly high MDA levels in TV (1.572 nM/ml) and PP (1.562 nM/ml) groups comparing to Sham (1.123 nM/ml) group. But in the Pre 2.5 (1.149 nM/ml) and Pre 5 (1.321 nM/ml) groups was lower indicating lowering of the oxidative stress (Diagram 4).

Blood MDA was more or less same in all groups: (Sham: 69.98 nM/ml; TV: 65.98 nM/ml; PP: 73.4 nM/ml; Pre 2.5: 71.97 nM/ml; Pre 5: 70.29 nM/ml). SH level was almost even (Sham: 42.38 nM/ml; TV: 45.25 nM/ml; PP: 44.92 n M/ml; Pre 2.5: 48.63 nM/ml; Pre 5: 42.92 nM/ml) (Diagram 5, Diagram 6).

p-AKT level after preconditioning was lower in TV group comparing to Sham, Pre 2.5 and Pre 5 groups demonstrating negative impact of the pneumoperitoneum and preventive effect of the preconditioning (

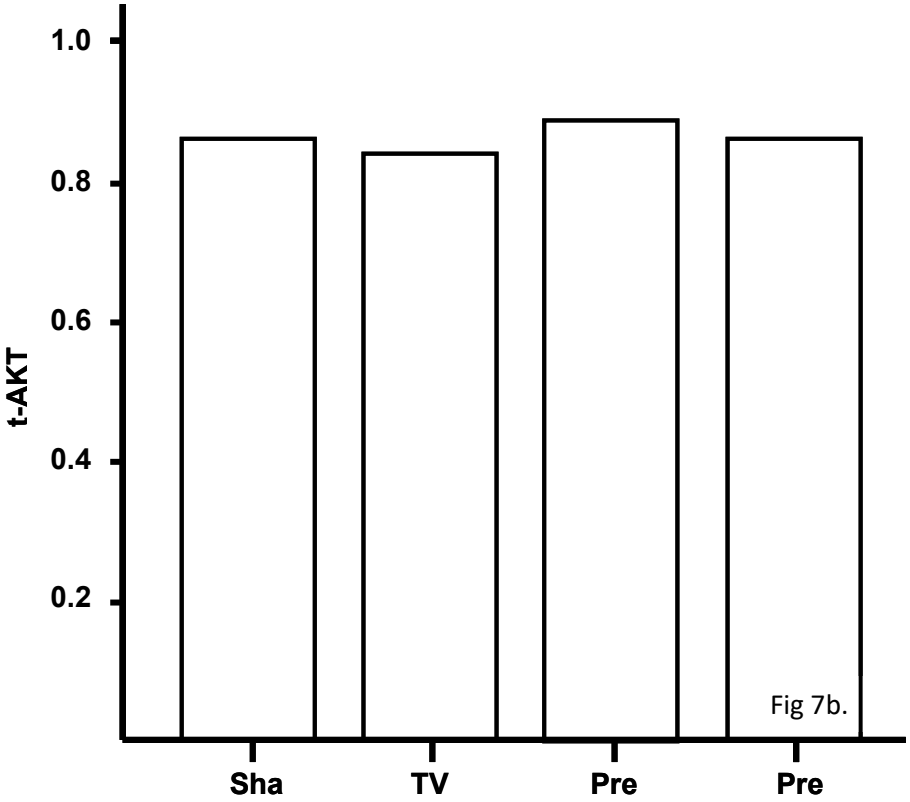


Diagram 7). Systemic inflammatory response caused by elevated intraabdominal pressure was shown by higher TNF-a levels in TV (29.62 pg/ml) and preconditioning groups (Pre 2.5: 32.86 pg/ml; Pre 5: 32.56 pg/ml) comparing to the Sham group (12.86 pg/ml). According our results preconditioning could not prevent it (Diagram 8).

Discussion

Laparoscopic technique has several advantages: less postoperative pain, shorter hospital stay, better wound healing, rear hernia formation. According several trials surgical trauma after laparoscopic procedures is lower than after open surgery.

Gál et al. studied the changes of MDA, GSH, GSSG (oxidized glutathione) IL-6 and CRP (C-reactive protein) after open and laparoscopic cholecystectomy. Pro-oxidant

marker levels ware lower after laparoscopy comparing to open surgery, demonstrating higher oxidative stress after open operation. The intensity of the oxidative injury correlates with the incision length [383–384].

Capnoperitoneum created for laparoscopic surgery has damaging impact. Increased intraabdominal pressure decreases tissue perfusion and results hypoxia. Released oxygen radicals damage intraabdominal organs.

Gutt and Schmandra measured blood flow in the intraabdominal organs during CO2 pneumoperitoneum with different intra-abdominal pressures (0–12 Hgmm) in rats. They proved that blood flow is reversely correlated with the intra-abdominal pressure and is minimal at 12 mmHg. Resulted hypoxia and oxygen radicals damage abdominal organs [385].

Akbulut et al. investigated result of the different duration CO2 pneumoperitoneum (120 and 240 minutes) in rats. They measured levels of the carbonyl- and sulfhydryl-groups and superoxide dismutase in the rat kidney tissue. Carbonyl-group level was elevated and sulfhydryl-group level and superoxide-dismutase activity were decreased in both 120 and 240 groups. Intensity of the oxidative stress was correlated with the duration of the pneumoperitoneum causing greater damage [386].

Emir et al. detected increased created xanthine-oxidase activity in small bowel and colon tissues after 20 minutes pneumoperitoneum in rabbits demonstrating intestinal damage caused by oxidative stress. [387].

Human observational studies confirmed damaging effect of the oxidative stress caused by pneumoperitoneum.

Markers of the oxidative stress -- MDA and sulfhydryl-group – were investigated by Polat et al. after laparoscopic cholecystectomy on 24 patients (12 male and 12 female). Markers were higher in 15 mmHg pressure group comparing 10 mmHg [388].

Our results indicate the similar consequences of the pneumoperitoneum. In our study reduced glutathione (GSH) level and superoxide-dismutase (SOD) activity and increased malondialdehyde (MDA) level after establishment of the pneumoperitoneum demonstrated development of the oxidative stress. Unchanged levels of the malondyaldehide (MDA) and sulfhydryl-group (SH-) could be explained by insufficient time of insult for affection of there levels [389].

The technique of the Veress needle insertion had no effect on the intensity of the oxidative stress (PP and TV groups).

Numerous studies investigate methods of the reduction of the oxidative stress caused by pneumoperitoneum. Preconditioning can reduce oxidative stress caused by increased intra-abdominal pressure. Yilmaz et al. studied oxidative stress reduction caused by pneumoperitoneum in rats using preconditioning. They measured inflammatory cytokines and oxidative stress marker, after created pneumoperitoneum and after preconditioning for 10 minutes. According this study preconditioning has a better effect than reducing intra-abdominal pressure From 15 to10 mmHg. Same authors erythropoietin as a protector from negative effects of pneumoperitoneum. According there data,

erythropoietin has a significant benefit but impact of the preconditioning was better [390, 391, 392, 393].

Sahin et al. attempted to reduce the negative effect of pneumoperitoneum by gradual rising the intra-abdominal pressure (5 mmHg for 10 minutes then 10 mmHg for 10 minutes and 15 mmHg pneumoperitoneum for 60 minutes). The elevation of the oxidative stress markers and inflammatory cytokines were indicating heavier injury in the gradual rising group compared to the Sham-operated group. In the 15 mmHg intraabdominal pressure group the oxidative damage and inflammatory reaction was larger then the stepwise gradual group [394].

The results of Yilmaz et al. [392] were used by us to employ preconditioning for protection. Following oxidative stress markers were studied: GSH, SOD, MPO and MDA. GSH and SOD concentration and activity were increased in the preconditioning groups compared to TV and PP groups. MDA level was also higher in TV and PP groups then in Sham and preconditioning groups. MPO level was higher in preconditioning groups then in TV and PP groups.

Ischemic preconditioning (IPC) was undertaken on isolated rabbit heart by Solenkova et al. IPC decreased extent of the myocardial infarction via kinases during reperfusion. They noticed that administration of the nonselective and selective adenosine receptor blocker immediately after ischemic insult completely abolishes protective effect of the preconditioning. They suggest that such phenomena could be mediated by activation of the p-AKT anti-apoptotic pathway by endogenous adenosine produced during ischemia [395]. Solenkova's study result motivated us to examine the anti-apoptotic pathway activation during pneumoperitoneum and preconditioning. We tested p-AKT level in rat kidney tissue which was lower in the

TV group then in the Sham and preconditioning groups. These results could indicate the activation of the apoptotic processes by pneumoperitoneum and mediation of the protective mechanism of the preconditioning via activation of p-AKT.

Pneumoperitoneum can activate systemic inflammatory response. This effect could not be reduced by preconditioning. In our study TNF-a level was greater than before in TV, Pre 2.5 and Pre 5 groups compared to the Sham group.

The results of our study demonstrate the damaging se findings demonstrate that pneumoperitoneum has a harmful consequences correlated with duration and intraabdominal pressure. Preconditioning could be able to reduce these negative effects and could be clinically significant preventive tool.

2. Effects of postconditioning on tissue ischemic injury

Materials and Methods

Animals

Sixty adult female Wistar rats, weighing 300±50g were used in this study. The animals were housed in cages where standard chow and water were available. The rats were fasted for 12 hours before any procedures. The studies were approved by the Local Committee for Animal Experimentation of University of Pecs, Hungary.

Anesthesia

The rats were anesthetized by intraperitoneal (i.p.) injection of ketamine (37.5 mg/kg) and seduced (3.75 mg/kg).

Study design

The animals were divided into four equal groups each consisting of 15 rats, which also were divided into four subgroups according to time of blood taking (n=5) (Table 1).In all cases besides sham group pneumoperitoneum was created by CO2 insufflation under a pressure of 10mmHg. Creation of pneumoperitoneum the Veress needle was placed into the abdominal cavity from the vaginal orifice which was connected by the polyethylene tube to insufflator (Karl Storz GmbH&Co. KG, Tuttlingen Germany). During the surgical procedures after the placed Veres needle in two cases were bleeding from outer part of vaginal orifice, no other kind of complications were noticed.

Study groups

Group 1: The sham-operation group. A Veres needle was placed into the vaginal orifice without any other surgical procedure or gas insufflation.

Group 2: Transvaginal pneumoperitoneum (TV/PP) was subjected to pneumoperitoneum for 60 min followed by 30 min of desufflation.

Group 3: Post-conditioning with 5 min. (Post-5) was subjected to pneumoperitoneum for 60 min plus by 5 min of desufflation and 5 min of insufflation followed by 30 min of desufflation.

Group 4: Post-conditioning with cycle (Post-cycle2.5) was subjected to pneumoperitoneum for 60min plus 2.5 min of desufflation and 2.5 min of insufflation repeated in two cycles followed by 30min of desufflation.

	Study Groups	Subgroups (according to time of blood taking)	Quantity-in Each Subgroups
1	Sham (n=15)	30min. 2h. 6h.	n=5
2	TV/PP (n=15)	30min. 2h. 6h.	n=5

3	Post-5 (n=15)	30min. 2h. 6h.	n=5
4	Post-cycle2.5(n=15)	30min. 2h. 6h.	n=5

Table 3. Animal groups of the postconditioning series

The rats were sacrificed from the last insufflation after the 30min, 2h, 6h. The blood samples were taken in each group after the above mentioned times from all animals by cardial punction and drown into the heparinized tubes. Oxidative stress markers such as: malondialdehyde (MDA), superoxide dismutase (SOD), reduced glutathione (GSH) and sulfhydryl groups (SH) levels as well as inflammatory cytokine TNF-alpha concentrations have been measured in all samples. Tissue samples of each intra-abdominal organ such as: liver, intestine, kidney and lung have been taken from every animal and were fixed in formalin.

Figure 17. Veres needle placement.

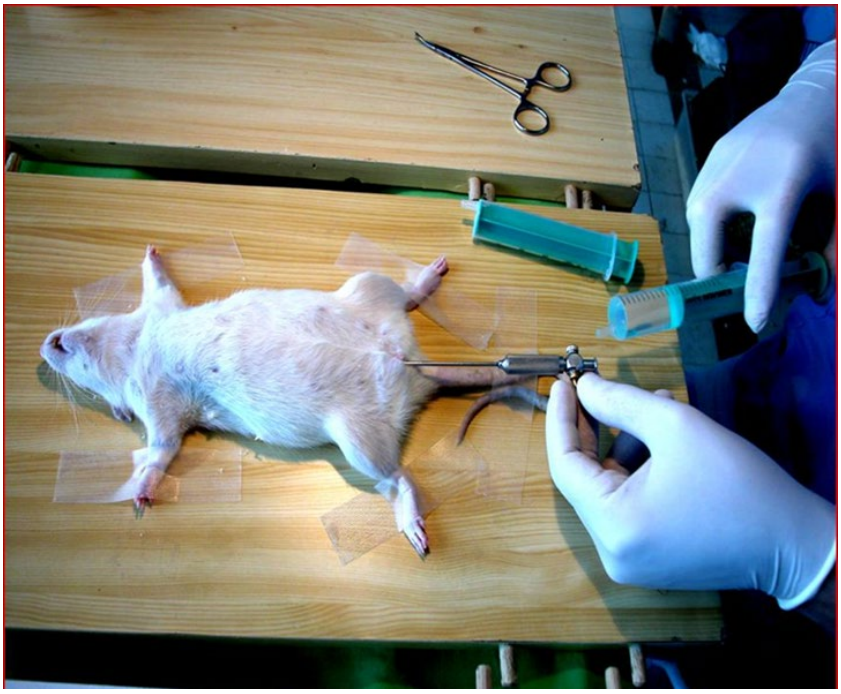


Figure 18. Checking needle position.

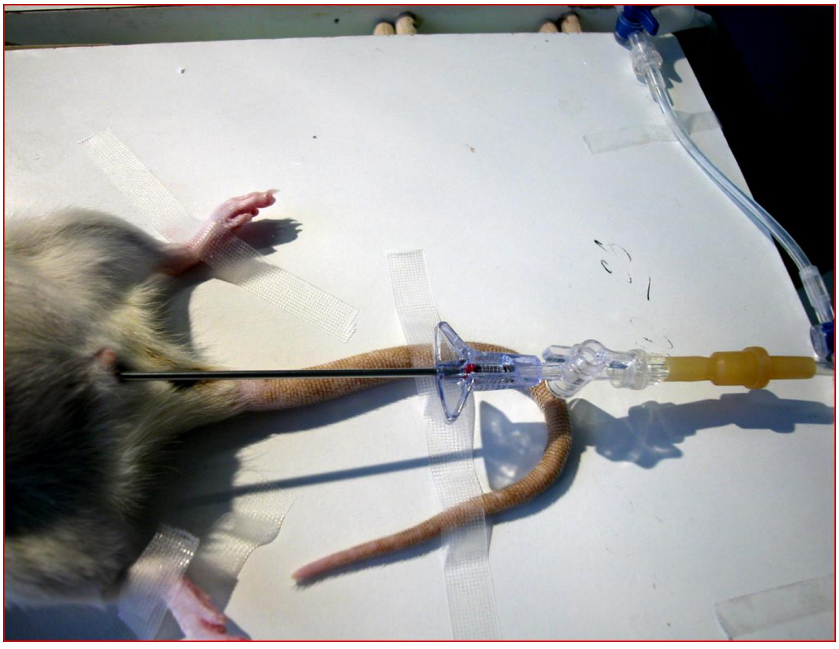


Figure 19.Veres needle fixation

Figure 20. Transvaginal pneumoperitoneum (TV/PP)

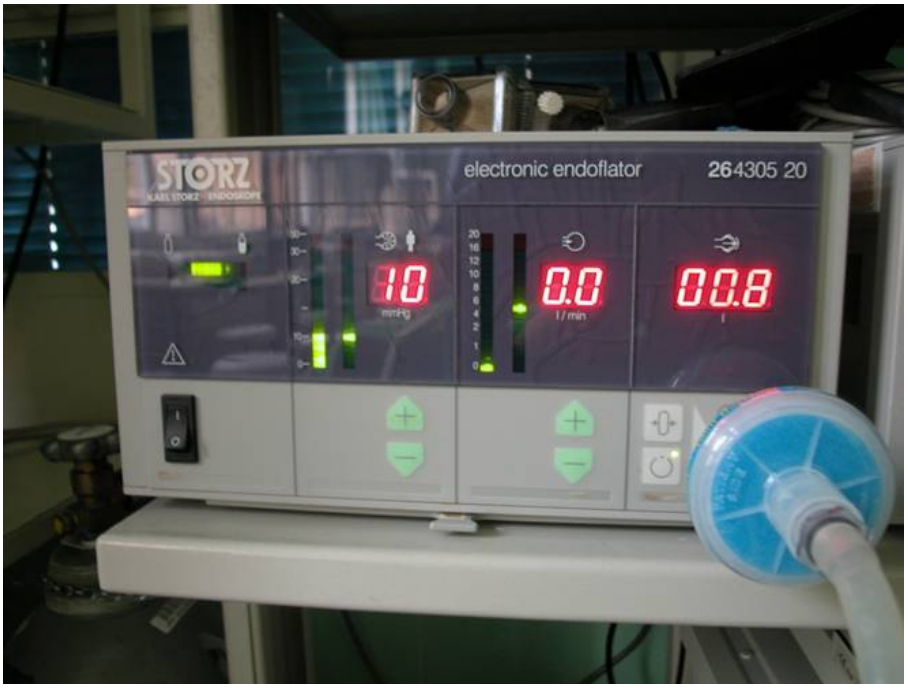


Figure 21. CO2 insufflation under a pressure of 10mmHg.

Figure 22. Taking blood samples.

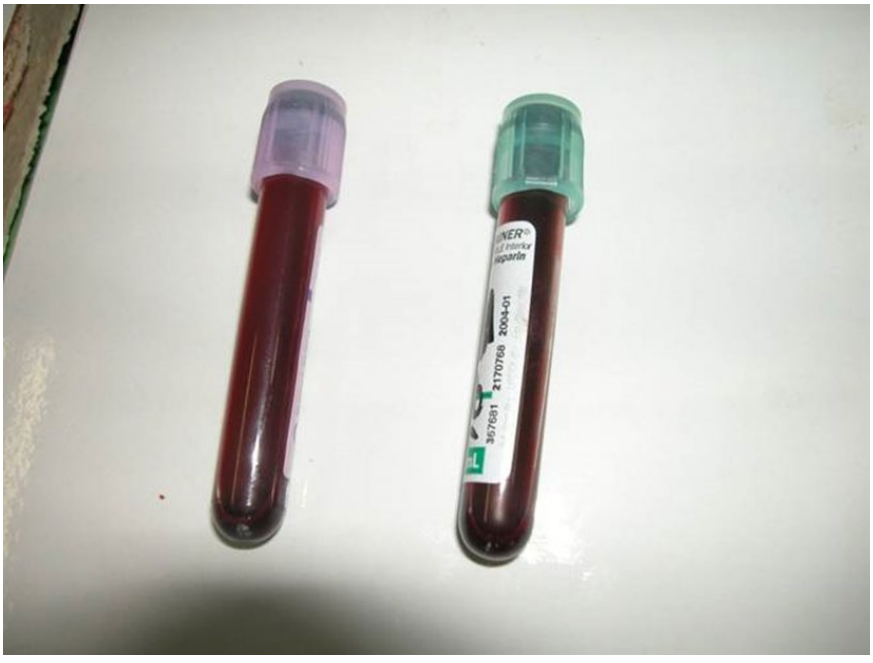


Figure 23. Blood samples.

Biochemical Assays

Detection of malondialdehyde (MDA) concentration:

To 0.5 ml diluted blood or plasma was added 4.5 ml thiobarbituric acid (TBA) and trichloroacetic acid (TCA) mixture. Sample was incubated at 100 ºC (in boiling water) for 20 minutes, and cooled in icy water. In cooled centrifuge blood was centrifuged for 15 minutes at 4000 rpm. Measurement with spectrophotometer was made at 532 nm. MDA concentration was calculated in nM/ml [396].

Detection of reduced glutathione (GSH) and sulfidril-group (SH-) concentration:

1 ml quintuple diluted blood sample and 4 ml trichloroacetic acid (TCA) mixture was used for determination. Mixture was centrifuged for 15 minutes at 400 rpm. 2 ml supernatant was added to 4 ml TRIS puffer (0,4 M, pH: 8.7) and immediately before measurement 100 µl 5,5'-ditio-bis-2-nitro-benzoe acid (DTNB) was added to mixture. Measurement with spectrophotometer was made at 412 nm. Concentration was calculated in nM/ml [397].

Detection of superoxide-dismutase (SOD) activity:

1 ml blood mixed with EDTA was used for SOD activity detection. 9 ml Hartman's solution was added to blood sample and centrifuged for 5 minutes at 2000 rpm. Washing procedure was repeated after the discarding of supernatant. 1ml chloroform and ethanol (2:1) mixture was added to 1 ml erythrocyte haemolysatum and centrifuged for 4 minutes at 17000 rpm.

Supernatant was separated and adrenalin (16.488 mg adrenalin diluted in 10 ml 0.1N hydrochloric acid) was added to supernatant and concentration was measured at 480 nm by spectrophotometer. Concentration was calculated in U/ml [398].

Detection of TNF-α concentration:

Detection was made using ELIS kit (Quantikine® Rat TNF-α/TNFSF1A Immunoassay, R&D Systems, Minneapolis, USA). Concentration was calculated in pg/ml.

Statistical Analysis:

Data are presented as mean ± standard error of the mean (SEM). For statistical analyses the non-parametric Mann-Whitney U test and one way ANOVA test were used. Significance was defined as $p<0.05$.

Results

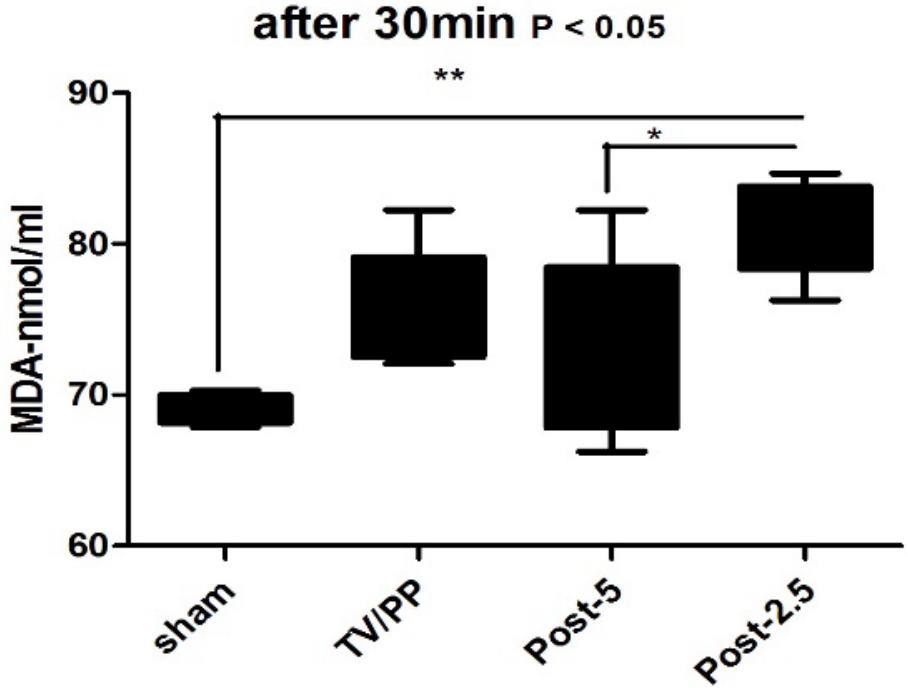
Malondialdehyd (MDA) determination (Diagram 9). Levels of malondialdehyd (MDA) in the Pp-post-5 group were significantly decreased after the 2 and 6 h compared with TT/PP and post-2.5 groups.

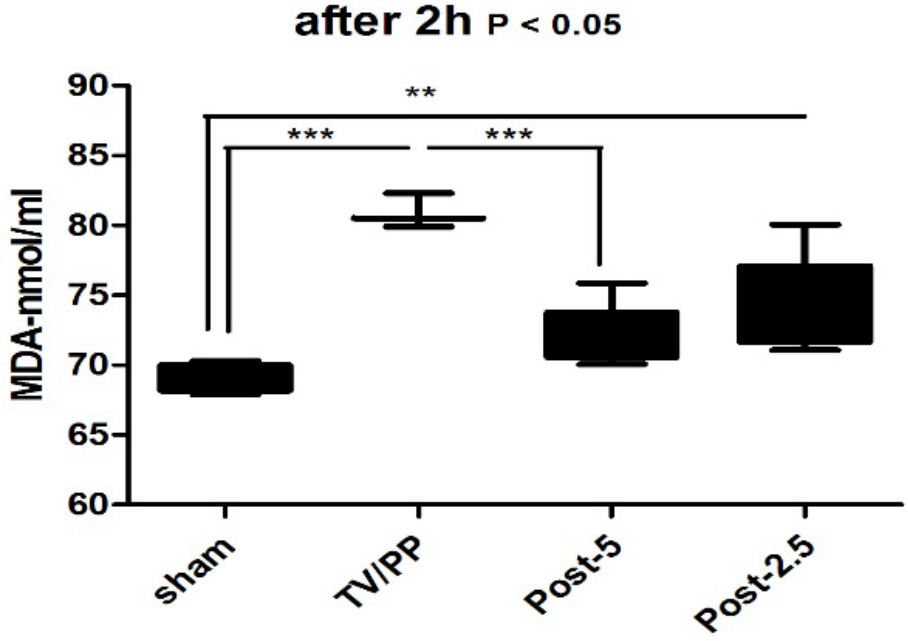
Reduced (GSH) determination (Diagram 10). We found that the GSH concentration in TV/PP group was significantly lower than in Sham and Post-5 group after the 30 min, after 2 end 6h there was not found any deference between the groups.

Sulfhydryl groups (SH) determination (Diagram 11) The SH-groups concentrations were significantly increased in Post-5 group compared with Sham, TV/PP and Post-2.5 groups after the 30min and 2 h.

Determination of superoxide dismutase (SOD) (Diagram 12). Activity of SOD showed no significant difference between the groups. (*–$P < 0.05$).

Determination of TNF-a concentration of TNF-α in case of TV/PP group was significantly higher than in Sham and postconditioning groups. ($P < 0.05$)


after 30min P < 0.05
**
*
90
80
70
60
MDA-nmol/ml
sham
TV/PP
Post-5
Post-2.5


after 2h P < 0.05
**
***
***
90
85
80
75
70
65
60
MDA-nmol/ml
sham
TV/PP
Post-5
Post-2.5

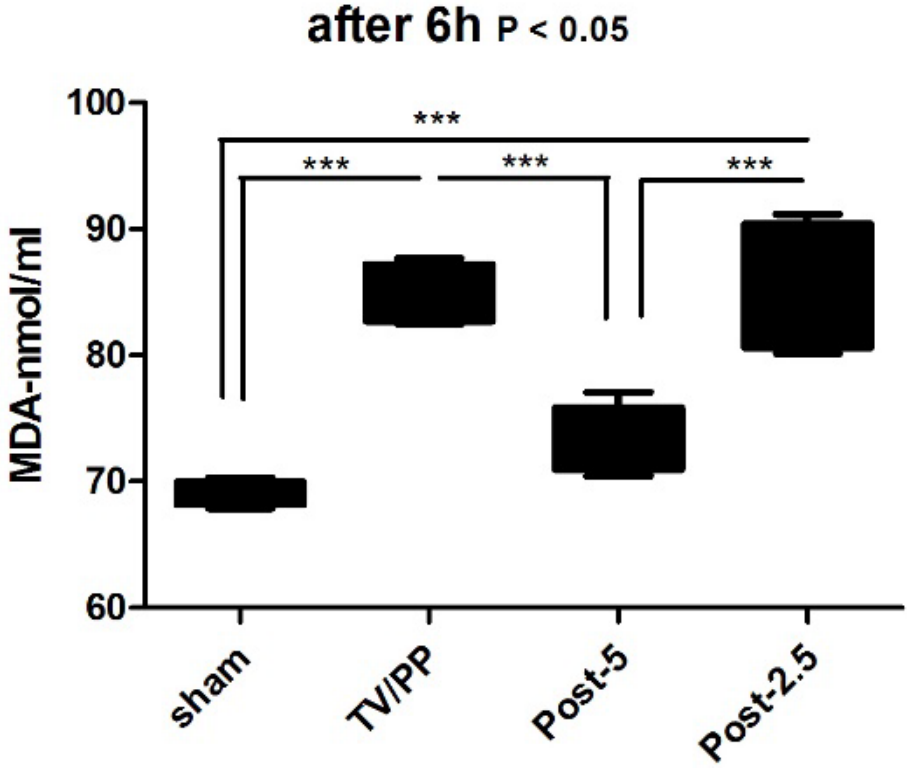


Diagram 9. Malondialdehid levels.

MDA concentration after the 2 and 6 h was significantly lower in the PP-post-5 group then in TT/PP and post-2.5 groups (*–P < 0.05).

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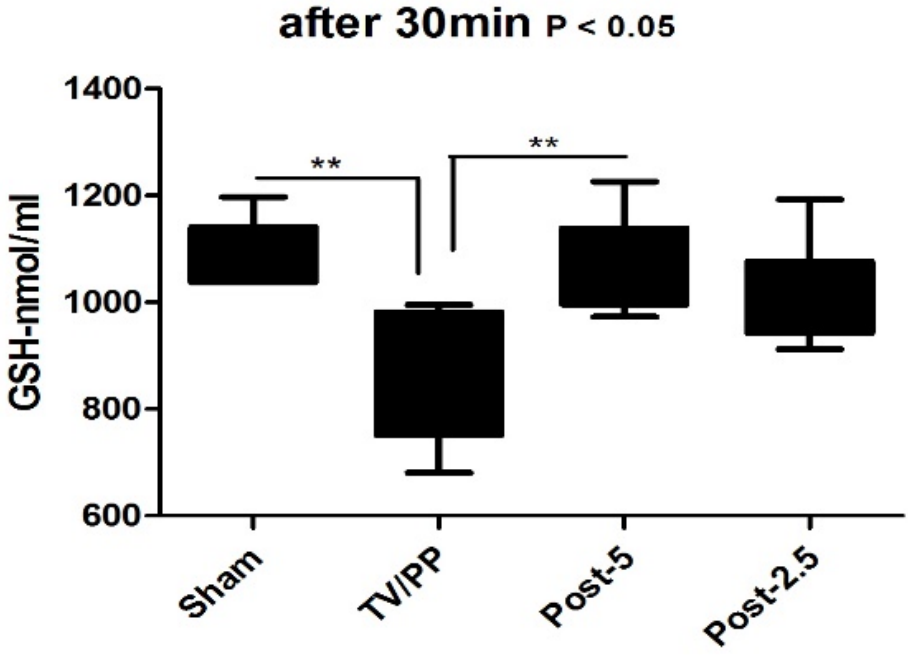

after 30min P < 0.05
GSH-nmol/ml
1400
1200
1000
800
600
**
**
Sham
TV/PP
Post-5
Post-2.5

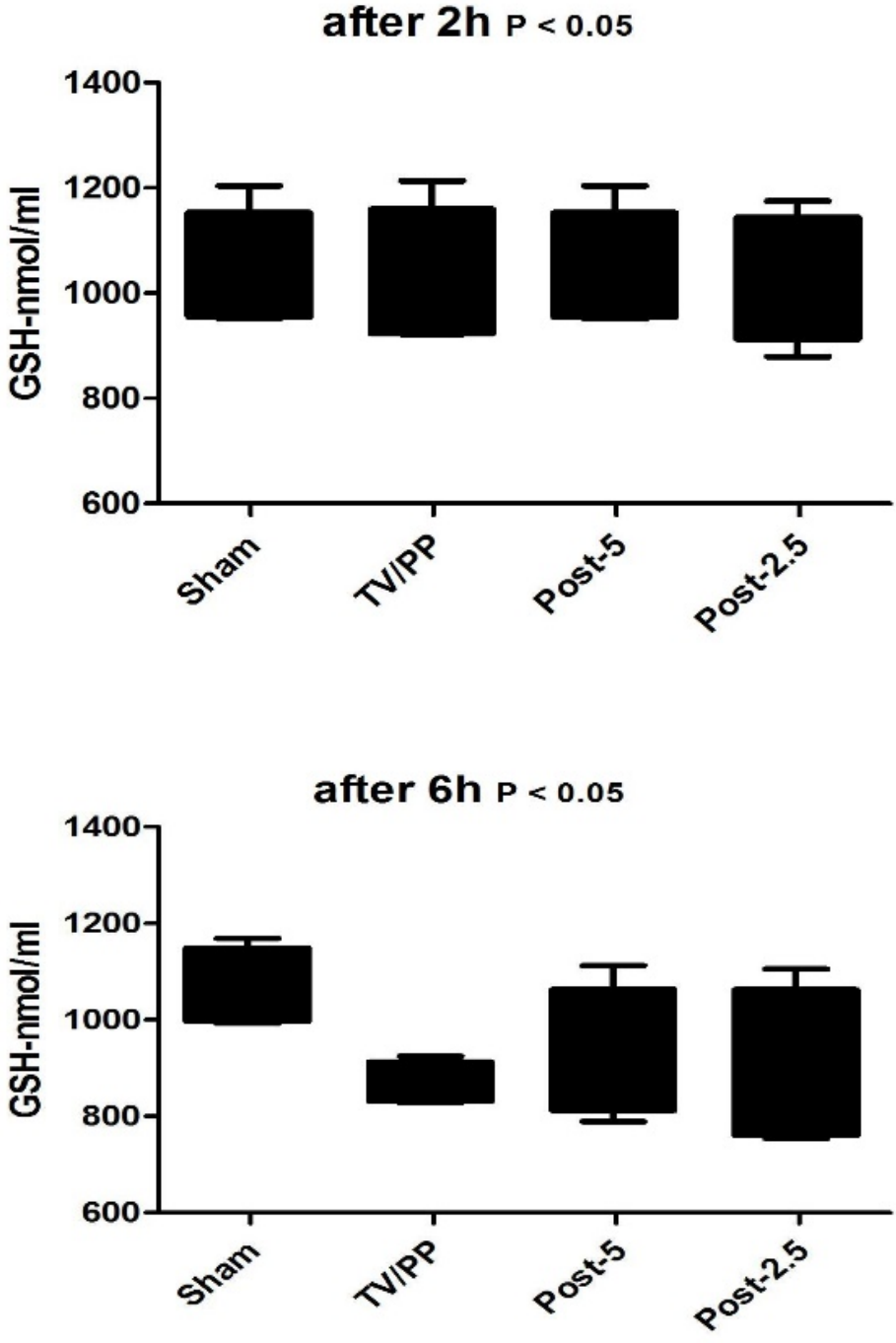
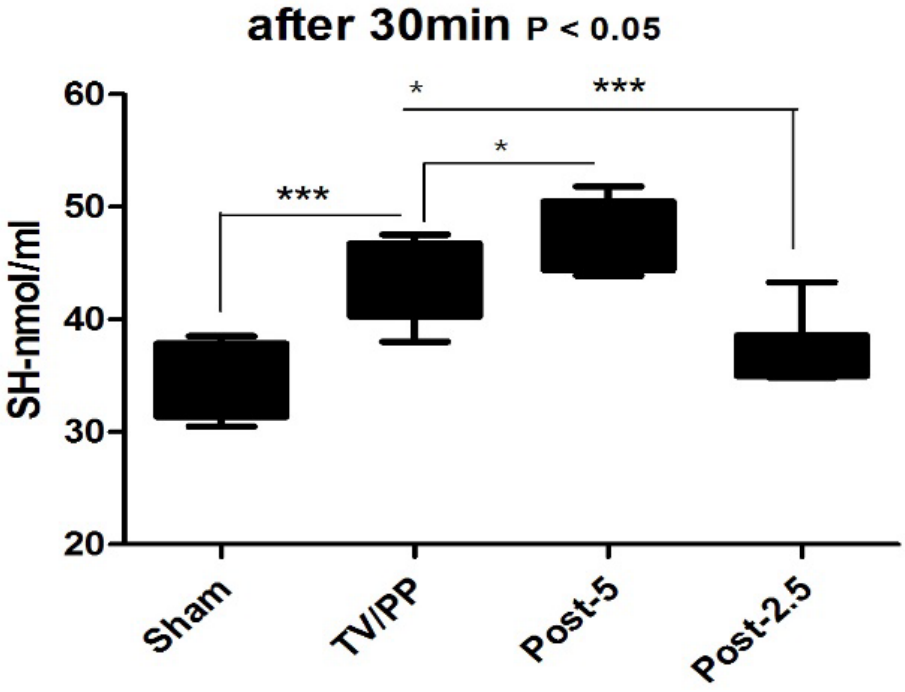


Diagram 10. GSH Levels. roups (*–P < 0.05).

After the 30 min GSH level was significantly decreased in in Sham and Post-5 group concentration in TV/PP groups, but there was no difference after 2 and 6h.


after 30min P < 0.05
SH-nmol/ml
60
50
40
30
20
*
***
*
***
Sham
TV/PP
Post-5
Post-2.5

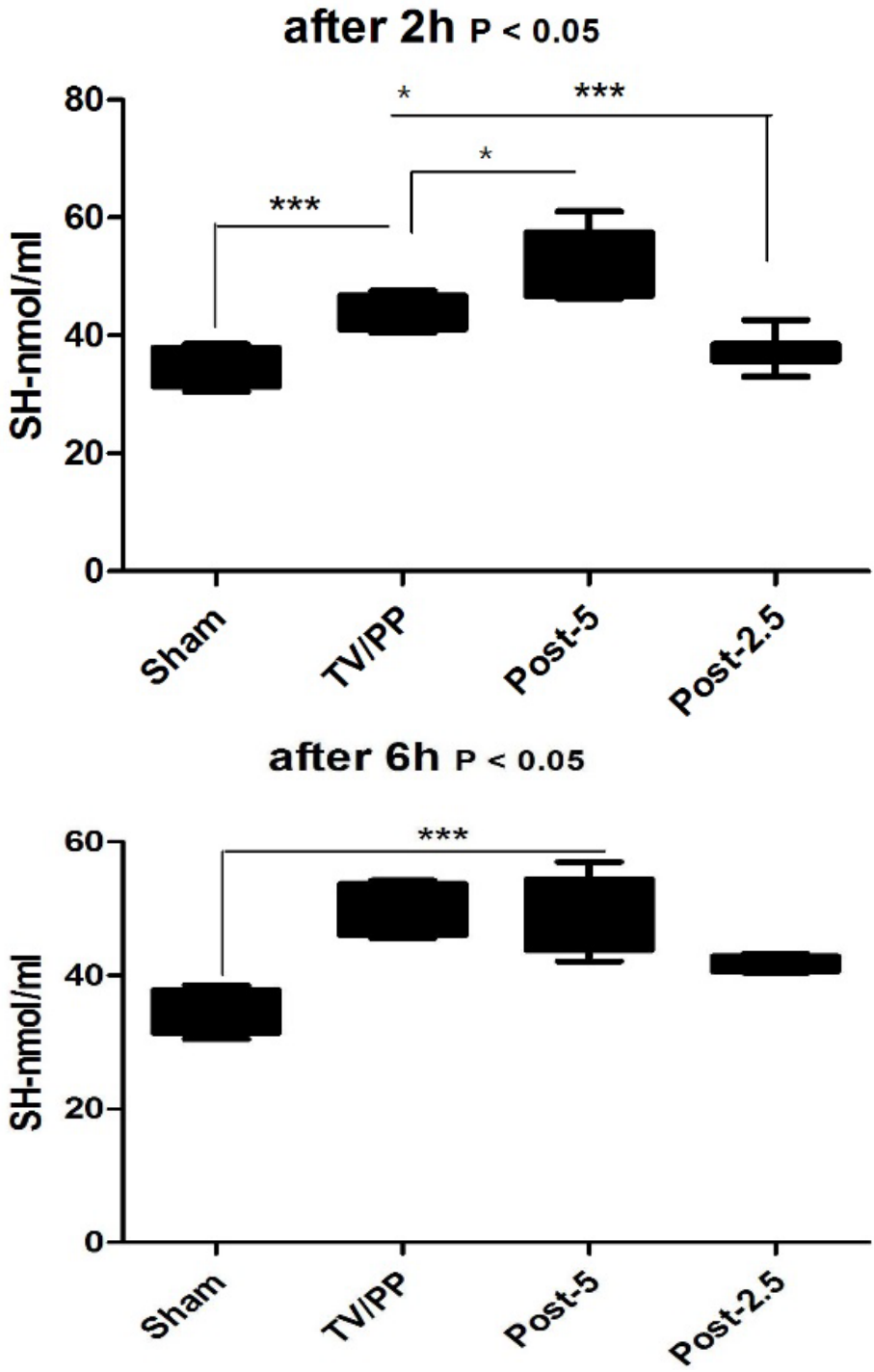
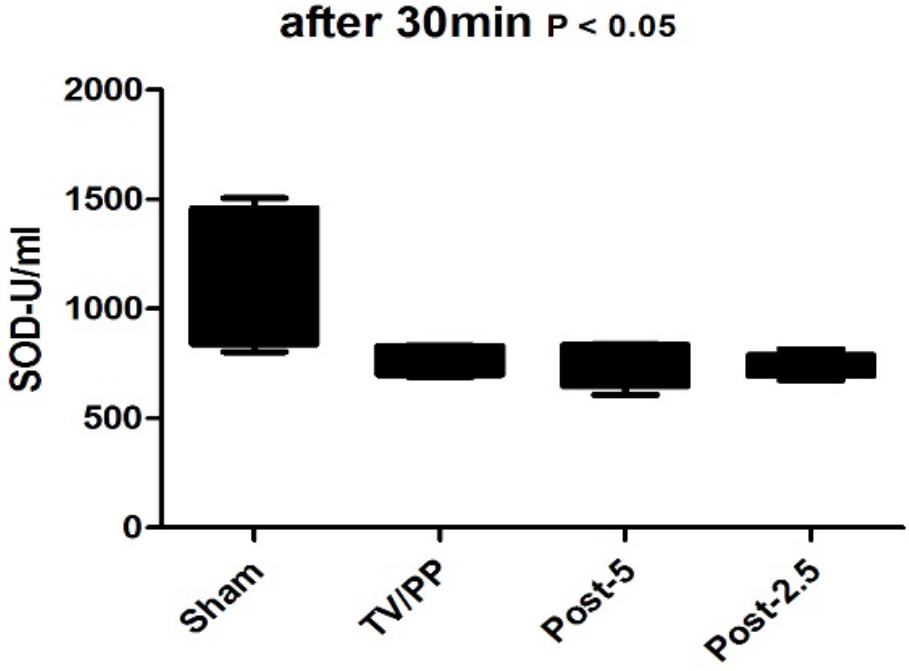
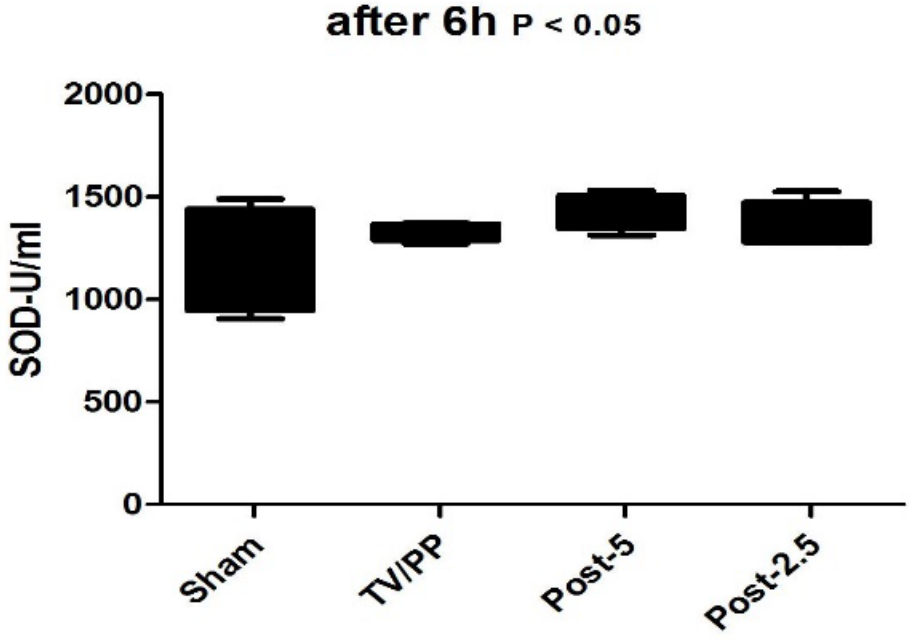


Diagram 11. SH-group levels.

After 30min and 2 h SH-groups level was significantly higher in Post-5 group than in Sham, TV/PP and Post-2.5 groups (*–$P < 0.05$).


after 30min P < 0.05
SOD-U/ml
2000
1500
1000
500
0
Sham
TV/PP
Post-5
Post-2.5


after 6h P < 0.05
SOD-U/ml
2000
1500
1000
500
0
Sham
TV/PP
Post-5
Post-2.5

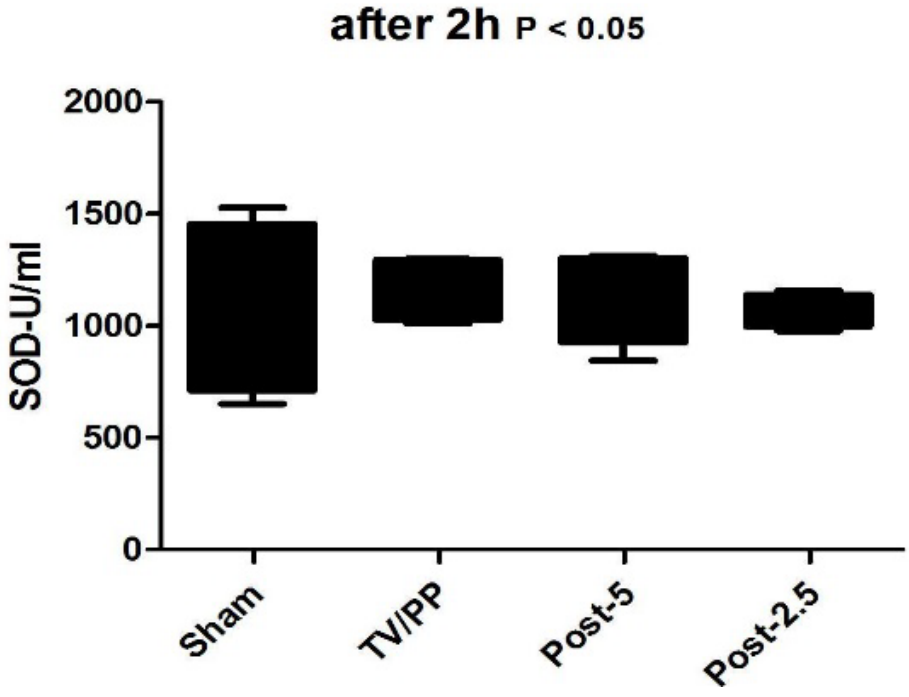


Diagram 12. SOD activity.
SOD activity was almost the same across groups (*–P < 0.05)..

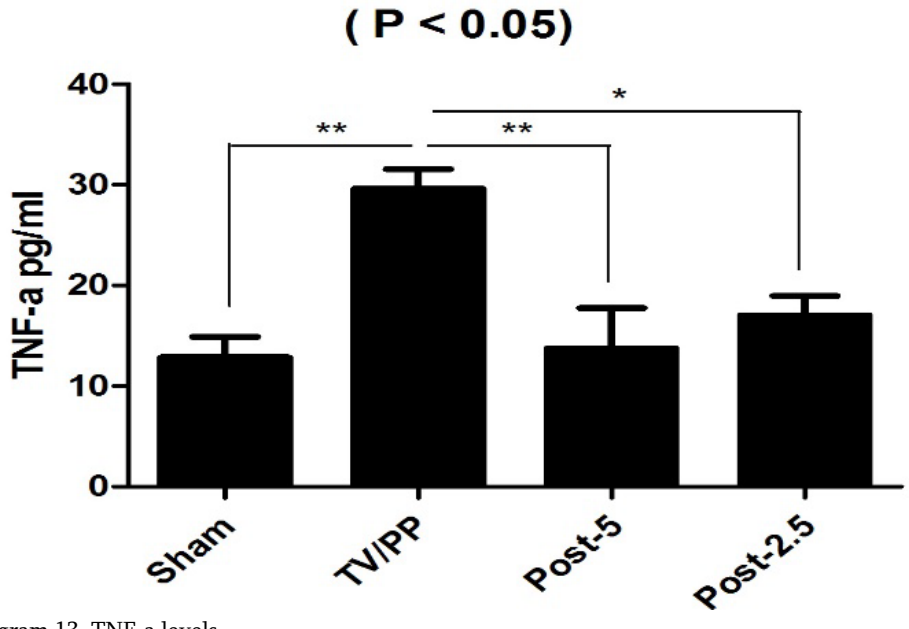


Diagram 13. TNF-a levels.

TNF-α level in TV/PP group was significantly higher than in Sham and posconditioning groups. ($P < 0.05$)

Discussion

It is known that during creation of pneumoperitoneum there is a cascade of chemical release occurring with peritoneal tissue stress, insult, and damage [399]. The proceeded hypo perfusion caused by the insufflation of abdominal cavity (under the pressure of 10 mmHg) may induce the ischemia and reperfusion (I/R) injury. The post-conditioning may have a protective effects. Hypothetically repetitive interruptions of tissues and organs blood flow applied immediately after a period of ischemia becomes tissues more resistant/tolerant to subsequent ischemic injury.

In our experiments the pneumoperitoneum was created by using the transvaginal approach owing to potential advantages of NOTES procedures associated with the less traumatic stress. In a study comparing the physiologic effects of NOTES with laparoscopy in a pig model Bingener et al. reported significant cardiopulmonary differences between the NOTES and laparoscopic group [400]. There are several reports about using the conditioning model to prevent the negative effects related to the pneumoperitoneum associated with respiratory, homeostatic and physiologic consequences [401, 402, 403]. The authors concluded that preconditioning can be more effective than low-pressure pneumoperitoneum in reducing the oxidative stress and inflammatory cytokine response associated with laparoscopy [404] and also preconditioning is more effective than the preischemic administration of erythropoietin in reducing the negative effects of oxidative injury [405]. K-X. Liu at. al. reported that combine method both preconditioning and immediate postconditioning has a protection against I/R injury caused by the pneumoperitoneum [406].

We used the postconditioning in the transvaginally created pneumoperitoneum for more efficacious of the method to decrease the negative effects of pneumoperitoneum. In our study the oxidative stress markers such as malondialdehyde (MDA), superoxide dismutase (SOD), reduced glutathione (GSH) and sulfhydryl groups (SH) levels as well as inflammatory cytokine TNF-a concentrations have been determined. Free radicals generate the lipid peroxidation process in an organism. Malondialdehyde (MDA) is one of the final products of lipid peroxidation in the cells. An increase in free radicals causes overproduction of malondialdehyde (MDA) [407]. As a result of our researches, the levels of malondialdehyd (MDA), after 30 min. was showed no significantly difference between the groups. After the 2h and 6h levels of malondialdehyd (MDA) in the post-5 group were significantly decreased compared with TT/PP and post-2.5 groups. In case of TT/PP group levels of malondialdehyd (MDA) were increased dynamically and maximum level was showed after the 6h. (Diagram 9)

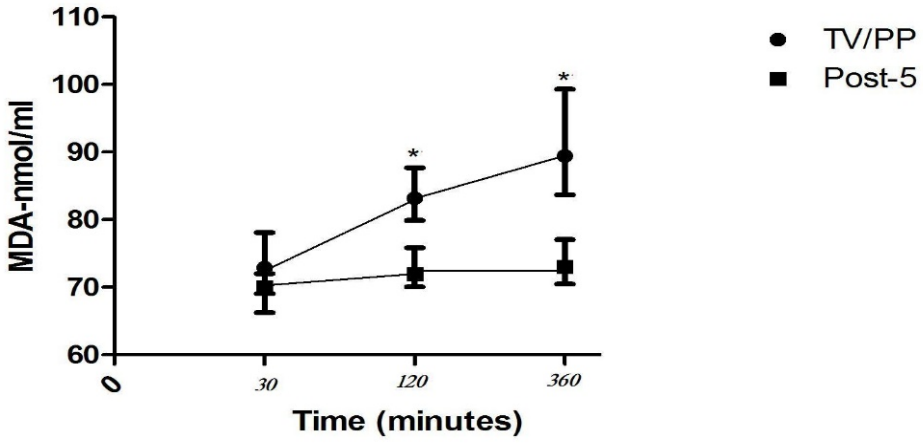


Diagram 14. Dynamical changes of the malondialdehyd levels (MDA).

It is known that the reduced glutathione (GSH) is major endogenous antioxidant produced by the cells, participating directly in the neutralization of free radicals and reactive oxygen compounds. Reactive oxygen species, overproduced at oxidative stress, are potent oxidizing and reducing agents that can directly damage cellular membranes by lipid peroxidation [408]. In this experiments the levels of reduced glutathione (GSH) after the 30 min. showed significantly difference between the groups, levels of reduced glutathione (GSH) in TV/PP group decreased significantly compared with Sham, Post-5 and Post-2.5 groups. After the 2h and 6h there were not significantly differences between the groups. We found no differences between the groups in case of activity the superoxide dismutase (SOD) . Sulfhydryl groups (SH) are considered as major plasma antioxidants in vivo and most of the SH-groups are present over albumin and are major reducing groups present in the body fluids, [409]. In case of sulfhydryl groups (SH) have demonstrated, that after the 30 min. and 2h the levels of this marker increased in Post-5 groups compare with Sham, TV/PP and Post-2.5 groups, after the 6h there were not significant differences between the groups besides Sham group. Cytokines, such as TNF-a, play key role in mediating the host inflammatory response.TNF-a is considered as a initial mediator of the cytokine cascade and appears to be the first cytokine into the blood stream. The release of TNF-a is inhibited following the hypoxia and reoxygenation periods [410].

In our study, after the pneumoperitoneum did not increase the level of TNF-a in groups of Post-conditioning than in TV/PP group.

Another important finding in our study is that the method of post-conditioning without cycles (Post-5) is more effective than post-conditioning with cycles (Post-2.5).

Our results confirmed that laparoscopic surgery using pneumoperitoneum inducing oxidative stress and causes the intra-abdominal organs damage. The postconditioning may reduce the oxidative injury after the created of pneumoperitoneum. These methods might have important clinical implications. But further investigations are necessary.

CONCLUSIONS

1. Pneumoperitoneum causes Ischemic insult, which could be detected by measuring the oxidative stress markers in rats.
2. Preconditioning decreases harmful effects of the oxidative stress caused by pneumoperitoneum in rats.
3. Postconditioning is easy maneuver which prevents damage caused by ischemia initiated by pneumoperitoneum in rats.
4. Pre- and postconditioning could get easy and effective prevention method against damaging impact of the pneumoperitoneum during surgical laparoscopy in clinical setting, however further investigations are necessary.

THEORETICAL AND PRACTICAL RECOMMENDATIONS

Pre - and postconditioning maneuvers may be effective in preventing measures against harmful effects of the pneumoperitoneum. It is necessary to check our results in clinical settings before routine application in the operating theatre. Pre- and postconditioning themselves contain minimal risk for the patient and is applicable for clinical study.

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