EXPERIMENTAL STUDY

Is the increased ozone dosage key factor for its anti-inflammatory effect in an experimental model of mesenteric ischemia?

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ABSTRACT

BACKGROUND: Ischemia/reperfusion injury of the intestines is a severe surgical condition. This study aimed to reveal ozone therapy effects with relatively increased ozone dosage in a created ischemia/reperfusion injury model.

METHODS: In this study, 24 albino Wistar rats were examined in three groups. Rats in the control group (CG, n=8) underwent only a laparotomy. In the sham group (SG, n=8) and ozone group (OG, n=8), the superior mesenteric artery (SMA) of the rats was occluded for 1 h. After de-occluding the SMA, the abdomen was closed, physiological saline was infused intraperitoneally in the SG, and an increased ozone/oxygen mixture dose (from 0.7 mg/kg to 1 mg/kg) was infused intraperitoneally in the OG. Small intestine samples were obtained at the 24th h for histopathological examination of intestinal mucosal injury and evaluated according to the Chiu score. In addition, Malondialdehyde and Myeloperoxidase levels were evaluated for oxidant levels, whereas, Glutathione (GSH) enzyme activity was measured to evaluate the tissue antioxidant system.

RESULTS: Histopathologically, the Chiu score was the lowest in the CG. It was lower in the OG compared to the SG showing the ameliorating effect of ozone on the intestinal mucosa. Chiu score in the OG was higher compared to that in the CG, but not statistically significant. A significantly higher GSH level was observed in the OG compared to the SG, proving antioxidant activity.

CONCLUSION: In this experimental model of ischemia/reperfusion in rats, treatment with an increased ozone level decreased the inflammatory process through antioxidant mechanisms and reduced intestinal mucosal damage. However, the effectiveness of ozone therapy depends on its dosages.

Keywords: Antioxidant; ischemia/reperfusion; ozone therapy.

INTRODUCTION

Ischemia/reperfusion of the intestines is a severe surgical condition in pediatric surgery. It commonly occurs in a child due to midgut volvulus, mesenteric thromboembolic events, or intussusception.[1] Ischemia/reperfusion injury is related to the development of microvascular dysfunction after the reperfusion of ischemic tissues. Activated endothelial cells in the microcirculation produce excess free oxygen radicals and less nitric oxide (NO) in the early reperfusion state. The abundant release of free oxygen radicals activates the inflammatory process, which worsens the clinical condition.[2] Various substances have been investigated to reverse this condition.[3] Ozone (O3) was recently investigated to promote antioxidant

Cite this article as: Erginel B, Yanar F, İlhan B, Yüksel S, Mikailo P, Berker B, Keskin E, Gün Soysal F. Is the increased ozone dosage key factor for its anti-inflammatory effect in an experimental model of mesenteric ischemia? Ulus Travma Acil Cerrahi Derg 2023;29:1069-1074.

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Ulus Travma Acil Cerrahi Derg 2023;29(10):1069-1074 DOI: 10.14744/tjtes.2023.86086 Submitted: 03.03.2023 Revised: 13.07.2023 Accepted: 25.07.2023

enzyme activity.[4] It activates antioxidant enzymes, improves blood circulation, and has several anti-inflammatory effects.[5,6] This study aimed to reveal ozone therapy effects in rats' created ischemia/reperfusion injury model by examining inflammatory and anti-inflammatory indicators and histological injury scores. We evaluated Myeloperoxidase (MPO), Malondialdehyde (MDA) since they are important markers of lipid peroxidation and increases in ischemia/reperfusion injury as an oxidant mechanism and Glutathione (GSH) since it is increased to combat the oxidant stress as the antioxidant mechanism.

MATERIALS AND METHODS

This study was approved by the Local Ethical Committee (Decision year/no: 2014/54) in the Institute of Experimental Medical Research and Application, İstanbul University, İstanbul Medical Faculty. The animals were housed under controlled temperatures (21±2°C), lighting (12-h light/dark cycle), and humidity. In the control group (CG, n=8), rats underwent only a laparotomy. In the sham group (SG, n=8) and ozone group (OG, n=8), the superior mesenteric artery (SMA) of the rats was occluded for 1 h. After de-occluding the SMA, the abdomen was closed, saline was infused intraperitoneally in the SG, and ozone therapy (1 mg/kg) was infused intraperitoneally in the OG. Small intestine samples were obtained at the 24th h for histopathological examination of intestinal mucosal injury and examined according to the Chiu score. In addition, the oxidative stress marker levels as MDA, GSH, and MPO were examined separately.

In the literature, 0.7 mg/kg ozone dose was used to examine its' antioxidant effects in previous and few intestinal ischemia/reperfusion injury models. In this study, it was aimed to investigate the effects of an increased ozone dose of 1.0 mg/kg in a similar experimental model.

Surgery

Ketamine (50 mg/kg) (Ketalar, Eczacıbası, Türkiye) and xylazine (20 mg/kg) (Kepro xylazine, Biopharm, Türkiye) were administered to induce anesthesia. The abdominal wall was shaved, and the skin was prepared with 10% Povidone-iodine (Isosol, Merkez Lab, Türkiye). A midline laparotomy was performed. In the CG, no additional procedure was not added to laparotomy. The SMA was dissected and occluded in the SG and OG with a micro-bulldog clamp for 1 h [Figures 1 and 2]. During the occlusion, the laparotomy wall kept approximated. One hour later, after de-occlusion, the abdominal wall is closed. In addition, 1 mL of physiologic serum was intraperitoneally administered to the animals in the SG, whereas 1 mg/kg ozone was intraperitoneally administered in the OG. The increased ozone dosage, which was thought to be more beneficial, was determined based on current literature.[7] All rats were fasted and killed 24 h following de-occlusion. Two centimeter specimens of the small intestine were resected (5 cm away from the terminal ileum) for histopathological and biochemical examinations.

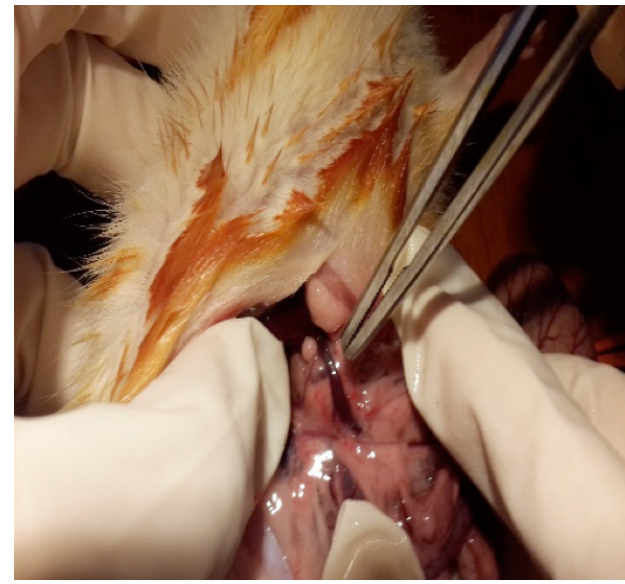

Figure 1. Dissection of SMA

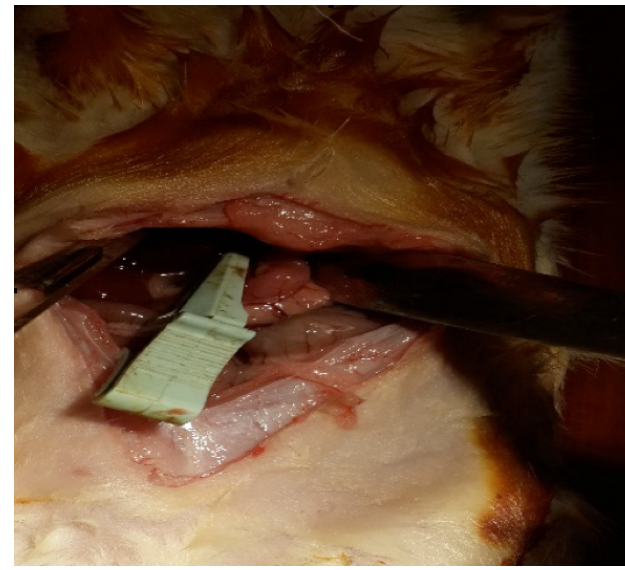

Figure 2. Occlusion of SMA

Biochemical Examination

Ileal tissue samples obtained and frozen at -80°C were used to evaluate the activities of MPO, MDA, and GSH.

Estimation of Tissue MPO Activity[8]

Tissues were homogenized in ice-cold phosphate-buffered saline (pH=6.0) with 0.5% hexadecyltrimethylammonium bromide. The obtained substant was centrifuged for 15 min at 40,000 × g (Eppendorf 5804R, Eppendorf, Hamburg, Germany). Clear upper supernatant fluid separated and assayed for MPO activity. MPO activity was analyzed spectrophotometrically at 460 nm/5 min absorbance. The concentrations of MPO were measured as nanograms per milligram protein (ng/mg protein).

Table 1. Histopathologic grades of intestinal tissue (Chiu scoring system)[11]

Grade	Histology
0	Normal mucosal villi
I	Development of a subepithelial space, usually at the tip of the villus, with capillary congestion
II	Extension of the subepithelial space with moderate lifting of the epithelial layer
III	Massive epithelial lifting down the sides of villi
IV	Denuded villi with lamina propria, dilated capillaries exposed, increased cellularity of the lamina propria
V	Digestion and disintegration of the lamina propria, hemorrhage, and Ulceration

Estimation of Tissue MDA Activity[9]

Tissues were homogenized in phosphate-buffered saline (pH=6.0) with 0.5% hexadecyltrimethylammonium bromide. The obtained substant was centrifuged for 15 min at 40,000 × g (Eppendorf 5804R;). Clear upper supernatant fluid separated and assayed for MDA activity. MDA activity was analyzed spectrophotometrically at 460 nm/5 min absorbance. The concentrations of MDA were measured as nanomoles per milligram protein (nmol/mg protein).

Estimation of Tissue GSH Content[10]

GSH levels in the tissue homogenates were measured using the Ellman reagent (5,5'- dithiobis-2-nitrobenzoic acid).

Histopathological Examination

Histopathological examination was performed by an experienced pathologist who was blinded to the groups. Tissues were fixed in a buffered 10% formalin solution for 24 h and embedded in paraffin. Ten consecutive longitudinal sections of 4-5-micron thickness were stained with hematoxylin and eosin. Light microscopy (Leica DMLS; Leica Camera AG, Wetzlar, Germany) was used to evaluate sections. In the histopathological examination, the scoring scale described by Chiu et al. was used.(Table 1).[11]

Statistical Analysis

The sample size was calculated with the G*Power Version 3.1.6 program. For the antioxidant levels measured in animal experiments between the groups, the difference in the medium effect size (effect size=1,0) was predicted to be statistically significant, and the sample size was determined as a total of 24 animals for 95% power at 0.05 alpha significance level. Descriptive statistical methods were used to analyze the results for the groups. The Shapiro-Wilk test was used for continuous variables with a normal distribution, whereas the Kruskal-Wallis test was used in 3 or more group comparisons of the variables showing non-normal distribution. The Mann-Whitney U-test was used for group comparisons that did not have normal distributions. P≤0.05 was considered statistically significant.

RESULTS

Biochemical Parameters

MPO activity

MPO activity was increased in the SG if compared with the CG. Intestinal MPO activity was lower in the OG than in the SG (P>0.05).

MDA levels

MDA level was increased in the SG if compared with the CG. On the other hand, the MDA level in the intestinal tissues decreased more in the OG than in the SG (P<0.05).

GSH levels

In our study, the GSH level, an indicator of the anti-inflammatory process, decreased significantly in the SG than in the ozone-treated group (P<0.05).

As the result, the median values of the biochemical parameters. MDA value was significantly lower in OG than SG, proving the decrease in oxidant activity after ozone therapy. GSH value was significantly higher in OG than SG, proving the increase in antioxidant activity after ozone therapy (Table 2).

Pathological parameters

A summary of the histopathological examinations of the in-

Table 2. Antioxidant levels

	MPO (nmol/min/mg)	MDA (nmol/min/mg)	GSH (nmol/min/mg)
Control1	0.70	21.95	12.35
Sham2	0.86	27.65	11.50
Ozone3	0.80	22.75*2-3	14.60*2-3

MPO: Myeloperoxidase; MDA: Malondialdehyde; GSH: Glutathione; 1: Control group; 2: Sham group; 3: Ozone group.

Table 3. The median values of the Chiu scores of the groups

	Chiu score
Control1	0 (0–1)*1-2
Sham2	2.5 (0–4)
Ozone3	1 (0–3)*3-2

testinal tissues according to the Chiu scoring system is presented in Table 3. The median Chiu score was higher in the SG than in the CG, and the Chiu score in the OG was lower than in the SG ($P<0.05$). Chiu score in the OG was higher compared to that in the CG, but not statistically significant ($P>0.05$).

DISCUSSION

Ischemia/reperfusion injury is a severe surgical problem in pediatric surgery clinics, usually following mesenteric ischemia. Reperfusion injury starts as soon as circulation is provided to the ischemic tissue. The return of circulation triggers an inflammatory process, causing the abundant release of reactive oxygen species. Molecular oxygen levels decrease as superoxide radicals are produced.[12] Many reports in the literature aim to minimize ischemia/reperfusion injury.[13,14] It has been demonstrated that ozone therapy may effectively reduce this oxidative stress and enable the production of more free oxygen radicals. Recently, ozone, an antioxidant that induces protective enzymes, has been studied in many conditions, such as peritonitis.[15] In addition, the beneficial effects of ozone therapy have recently been studied under various ischemic conditions, such as ovarian, testicular, and skeletal muscle injuries caused by tourniquets.[16-18] Based on the anti-inflammatory and antioxidant effects of ozone therapy, we aimed to evaluate the beneficial effect of ozone therapy in mesenteric ischemia in a rat model.

Haj et al. previously studied ozone therapy in ischemia/reperfusion in terms of mucosal damage.[19] They found that treatment with ozone in ischemia/reperfusion might result in a decrease in mucosal injury and apoptotic scores and significant increases in cell proliferation rates.

MDA and MPO activity has been investigated in various studies to show oxidative stress in tissues[20] and GSH enzyme activity has been measured to evaluate the tissue antioxidant system.[21]

MPO is a specific enzyme in the lysosomes of neutrophils.[22] In the present study, the increased MPO levels during ischemia/reperfusion were relatively decreased in the OG compared to SG, proving the decrease in neutrophil accumulation due to the antioxidant effect of ozone.

MDA is a stable lipid peroxidation product, indicating increased oxidative stress.[23,24] In our study, we evaluated tissue MDA levels after reperfusion. We detected increased MDA levels in the SG compared with the CG, indicating increased oxidative stress.

In addition, a slight decrease in the MDA levels occurred in the OG compared with the SG, showing an antioxidant effect in the OG. Senyucel et al. stated that the antioxidant effect might be related to whether the tissues with ischemic injury are treated with ozone for a sufficient time.[25]

Under normal conditions, reactive oxygen species are neutralized by endogenous antioxidant enzymes. Superoxide dismutase (SOD) and GSH are the best-known antioxidant enzymes.[12] Abbasoğlu et al. also studied these two enzymes in evaluating the taurine and carnosine effects on experimental testicular ischemia/reperfusion injury.[26] In our study, the GSH levels in the OG were elevated compared with those in the SG. GSH has been used to indicate antioxidant systems in evaluating various substances in such an ischemia/reperfusion model.[27] As in the study of Buetler et al., increased GSH levels were elevated as a defense mechanism against increased free oxygen radicals.[10]

We also aimed to evaluate the histopathological alterations caused by ozone therapy. Intestinal ischemia/reperfusion caused an increase in the Chiu score in the intestines. Therefore, the Chiu score was higher in the SG than in the CG. The OG had a slightly lower Chiu score than the SG did. Chiu score in the OG was higher compared to that in the CG, but not statistically significant.

Following the publication of the success of ozone therapy Dere Günal et al. also wanted to explore the use of ozone therapy in the treatment of ischemia and reperfusion as we did.[28] In our study, MDA, GSH, and MPO were examined to evaluate antioxidant capacity. In contrast, they studied NO and SOD in terms of oxidative stress markers in their study. In this simultaneous study, they reported that ozone therapy did not increase antioxidant enzymes and did not reduce oxidative stress. However, our results are different from this in antioxidant levels and histopathological findings. We think the reason for their different results is that two animals were less in each group in their study, and their ozone dose of 0.7 mg/kg (whereas we gave 1mg/kg) was insufficient to provide the effective dosage. The conclusion section emphasized the need for further research with different ozone therapy doses. We have revealed its effectiveness by increasing the ozone dose given in this study.

Already Chirumbolo et al. have investigated the mechanism of action of ozone therapy against COVID-19 in great detail.[29] Their studies concluded that ozone therapy reduces all kinds of ischemia/reperfusion damage by triggering the antioxidant system. However, they said that ozone dose plays a decisive role in this effectiveness. Therefore, they stated that the correct ozone protocol should be started to provide sufficient ozone gas benefits. While Dere Günal et al. could not see an increase in the antioxidant system by giving 0.7 mg/kg ozone in ischemia/reperfusion injury, Onal et al. applied

preconditioning before ischemia/reperfusion by giving ozone at a dose of 1 mg/kg for 5 days as we did and they saw its benefit.[7] Another significant difference between our study and Dere Günal et al. is that they evaluate the SOD instead of GSH activity to evaluate the antioxidant system. SOD and GSH are essential markers to evaluate the antioxidant system. While we saw an increase in GSH after ozone therapy, they did not detect an increase in SOD value, which may be because ozone treatment performs its antioxidant property through GSH.

One of the limitations of our study may be that many studies have been conducted on ischemia/reperfusion, and few studies evaluating ozone therapy in ischemia and reperfusion was also conducted. However, more studies are needed to determine the dosage of ozone therapy in ischemia/reperfusion injury. Mesenteric ischemia is the most common cause of short bowel syndrome, and its management is still a dilemma. For ozone therapy, more studies are needed to determine the protocols regarding dose, route of administration, and administration time to benefit from its clinical use. In addition, it should of course be kept in mind that the results obtained in experimental animal studies cannot be fully matched with the effects on humans.

CONCLUSION

Our study demonstrates that ozone therapy in this experimental model is safe and effective and yields promising results. These outcomes support ozone therapy usage in clinical ischemia/reperfusion conditions. However, the effectiveness of ozone therapy depends on its dosages. Further clinical studies are needed for constructing ozone protocols.

Ethics Committee Approval: This study was approved by the Experimental Medical Research and Application, İstanbul University, Ethics Committee (Date: 20.02.2014, Decision No: 2014/54).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: B.E.; Design: B.E.; Supervision: E.K., F.G.S.; Materials: B.E.; Data collection and/or processing: B.E.; Analysis and/or interpretation: B.E., F.Y., S.Y., P.M., N.B., B.İ.; Literature search: B.E.; Writing: B.E.; Critical review: E.K., F.G.S.

Conflict of Interest: None declared.

Financial Disclosure: The author declared that this study has received no financial support.

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DENEYSEL ÇALIŞMA - *ÖZ*

Yüksek ozon dozu, deneysel mezenter iskemi modelinde antiinflamatuar etkisi için anahtar faktör müdür?

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AMAÇ: Bağırsakların iskemi/reperfüzyon yaralanması ciddi bir cerrahi durumdur. Bu çalışma, oluşturulan bir iskemi/reperfüzyon yaralanması modelinde nispeten artan ozon dozu ile ozon tedavisinin etkilerini ortaya koymayı amaçlamıştır.

GEREÇ VE YÖNTEM: Bu çalışmada 24 adet albino Wistar rat üç grupta incelendi. Kontrol grubundaki sıçanlara (KG, n=8) sadece laparotomi uygulandı. Sahte grupta (SG, n=8) ve ozon grubunda (OG, n=8) sıçanların superior mezenterik arteri (SMA) 1 saat süreyle tıkandı. SMA deoklüzyondan sonra karın kapatıldı, SG'de intraperitoneal olarak fizyolojik salin infüze edildi ve OG'de intraperitoneal olarak artan ozon/oksijen karışım dozu (0.7 mg/kg'dan 1 mg/kg'a) infüze edildi. Bağırsak mukozal hasarın histopatolojik incelemesi için 24. saatte ince bağırsak örnekleri alındı ve Chiu skoruna göre değerlendirildi. Ayrıca oksidan düzeyler için Malondialdehit (MDA) ve Miyeloperoksidaz (MPO) düzeyleri, doku antioksidan sistemini değerlendirmek için ise Glutatyon (GSH) enzim aktivitesi ölçüldü.

BULGULAR: Histopatolojik olarak Chiu skoru KG'de en düşüktü. Ozonun bağırsak mukozası üzerindeki iyileştirici etkisini gösteren OG'de SG'ye kıyasla daha düşüktü. OG'deki Chiu skoru, KG'ye kıyasla daha yüksekti, ancak istatistiksel olarak anlamlı değildi. OG'de SG'ye kıyasla önemli ölçüde daha yüksek bir GSH seviyesi gözlendi ve bu da antioksidan aktiviteyi kanıtladı.

SONUÇ: Sıçanlarda iskemi/reperfüzyonun bu deneysel modelinde, artan ozon seviyesi ile tedavi, antioksidan mekanizmalar yoluyla inflamatuar süreci azalttı ve bağırsak mukozal hasarı azalttı. Bununla birlikte, ozon tedavisinin etkinliği dozajlarına bağlıdır.

Anahtar sözcükler: iskemi/reperfüzyon, ozon tedavisi, antioksidan

Ulus Travma Acil Cerrahi Derg 2023;29(10):1069-1074 DOI: 10.14744/tjtes.2023.86086