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Research Article

Effects of Hyperbaric Oxygen Treatment on Gastrointestinal and Hepatic Inflammatory Response After Subarachnoid Hemorrhage: an Experimental Study

Fethi GUL[1], Beliz BİLGİLİ[2], Husniye HACIOGLU BAY[3], Deniz FİLİNTE[4], Özgür ÇELİK[5], Ismail CİNEL[2]

[1]Marmara Üniversitesi Pendik Eğitim ve Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Kliniği, İstanbul, Turkey [2]Marmara Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon AD, İstanbul, Turkey [3]Marmara Üniversitesi, Anatomi AD, İstanbul, Turkey [4]Marmara Üniversitesi, Patoloji AD, İstanbul, Turkey [5]Marmara Üniversitesi, Beyin ve Sinir Cerrahisi AD, İstanbul, Turkey

Summary

Objective (Background): To investigate whether experimental subarachnoid hemorrhage (SAH) could induce histopathologic changes and inflammatory response in the gastrointestinal system, and if this response may be attenuated by the potential effects of hyperbaric oxygen therapy (HBOT).
Methods: Twenty rabbits were randomly divided into four groups. Group I was not subjected to SAH or sham operation. Group II were subjected to a sham operation. Group III were subjected to SAH and did not receive HBOT after SAH. Group IV were subjected to SAH and received five sessions of HBOT. Animals were euthanized through perfusion and fixation 72 h after the procedures. Four-millimeter tissue sections were obtained from the liver and terminal ileum and were examined microscopically. Arteriolar diameters were measured under light microscopy in five different examples taken randomly from each tissue. Statistical comparisons were performed using the Mann- Whitney U test.
Results: Increased inflammation was seen in the liver and terminal ileum in the SAH group compared with the sham and control groups. Inflammation in the SAH group was high compared with the HBOT group, but it did not reach significance. There were no differences between groups regarding edema.
Conclusions: We showed that HBOT performed after induced SAH was ineffective in the attenuation of inflammation in the liver and ileum tissues that occurred after SAH.

Key words: Subaracnoid hemorrhage, hyperbaric oxygen therapy, inflammation, ileum, liver

Subaraknoid Kanama Sonrası Gastrointestinal ve Hepatik Sistemde Gelişen İnflamatuar Yanıt Üzerinde Hiperbarik Oksijen Tedavisinin Etkileri: Deneysel Çalışma

Özet

Giriş: Bu çalışmada deneysel SAK modelinde gelişebilecek gastointestinal inflamatuar yanıt ve histopatolojik değişiklikler üzerinde hiperbarik oksijen tedavisinin azaltıcı etkisi araştırıldı.
Materyal ve Metod: 20 adet tavşan randomize 4 gruba ayrıldı. Grup I deki deneklere herhangi bir işlem uygulanmadı ve kontrol grubu olarak alındı . Grup II deki deneklere tedavi uygulanmayıp sham grubu olarak alındı. III.grupta SAK oluşturuldu. IV.grupta SAK oluşturulduktan sonra toplam 5 kez HBOT uygulandı. İşlemden 72 saat sonra çalışmaya alınan tüm hayvanlara perfüzyon-fiksasyon yöntemi ile ötanazi uygulandı. Karaciğer ve

terminal ileum alındıktan sonra 4 mm'lik kesitler elde edilerek dokular mikroskopik olarak incelendi. Yine her bir dokudan randomize alınan 5 farklı örneğin ışık mikroskopisi altında arteriolar çapları ölçüldü. Tüm sonuçlar Mann- Whitney U testi kullanılarak istatiksel olarak analiz edildi.
Bulgular: SAK grubunda kontrol grubuna göre karaciğer ve ileumda inflamasyon artışı anlamlı idi. HBOT grubu ile karşılaştırıldığında ise anlamlı inflamasyon değişikliği gözlemlenmedi. Gruplar arasında ödemde anlamlı farklılık izlenmedi.
Sonuç: Çalışmamızda SAK sonrası karaciğer ve ileum dokusunda gelişen inflamasyonun uygulanan HBOT ile gerilemediği gösterildi.

Anahtar Kelimeler: Subaraknoid kanama, hiperbarik oksijen tedavisi, inflamasyon, ileum, karaciğer Subaraknoid kanama, hiperbarik oksijen tedavisi, inflamasyon, ileum, karaciğer

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a pathologic condition that results from arterial blood flowing into the subarachnoid space of the brain. The extravasated blood prompts the release of various inflammatory factors and vasoactive molecules. The inflammation in response to subarachnoid blood is a pathway that leads to cerebral vasospasm (1). Accumulating evidence suggests that SAH triggers an inflammation cascade and disruption of blood brain barrier (BBB) facilitates systemic inflammation. This phenomenon contributes to the development of extracerebral organ dysfunctions, and it was recently suggested that SAH-induced neuroinflammation had a positive correlation with end-organ injuries (2,3).

The combination of brain injury and extracerebral organ dysfunctions after SAH adversely affect patient outcomes. Although SAH-induced acute brain injury accounts for principal morbidity and mortality, recent investigations recognized the importance of extracerebral dysfunctions in the acute period of injury (4,5). Metabolic, cardiac, and pulmonary complications are the best known secondary extracerebral complications after SAH (6,7). Besides these complications, gastrointestinal and hepatic dysfunction can be observed, such as gastrointestinal bleeding, decreased intestinal peristalsis, gastric reflux, and liver dysfunction. Gastrointestinal dysfunction can induce a cascade of events, such as intestinal cytokine overproduction, increased intestinal permeability, and translocation of intestinal bacteria and endotoxins, which leads to sepsis and septic shock (8-10).

Hyperbaric oxygen therapy (HBOT) is a useful approach for relieving acute ischemia and delayed cerebral vasospasm after SAH. HBOT has a neuroprotective effect by reducing oxidative stress, decreasing lipid peroxidation, and inhibiting endothelial apoptosis.11 Additionally, it reduces inflammatory processes by reversing adhesion of biologic molecules to the endothelial cell surface and preservation of nitric oxide-releasing neurons (11,12). Positive neurologic outcomes of HBOT have been demonstrated; amelioration of neurologic deficits and improvement of cognitive functions can be seen clinically (11).

AIM

Although the protective effect of HBOT after SAH has been shown for both cerebral hemispheres, the extracerebral effects of HBOT are still unknown. This study investigates the hypothesis that experimental SAH could induce histopathologic changes and an inflammatory response in the gastrointestinal system, and the inflammatory response may be attenuated by the potential effects of HBOT.

MATERIAL AND METHODS

Animals

The protocol for this study was approved by the Animal Research Ethics Committee of Marmara University. Twenty male New Zealand White rabbits weighing 2800-3200 grams were kept under standardized temperature (22±1°C) and humidity conditions with a 12-h:12-h light:dark cycle. The animals had free access to food and water and not fasted prior to experiments.

Anesthesia, analgesia, biomonitoring, and surgical procedures

A total of 15 animals in sham, SAH, and treatment groups underwent surgical procedures. Rabbits were anesthetized using an intramuscular injection of 60 mg/kg ketamine (Ketalar, Eczacıbası) and 15 mg/kg xylazine (Rompun, Bayer). All animals breathed spontaneously during the procedures. Systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP) were continuously recorded via a femoral artery catheter, which was connected to a pressure transducer and displayed on a monitor. Arterial blood gasses were analyzed during the procedures, and parameters were maintained within the physiologic range. Oxygen saturation was continuously recorded using a pulse oximeter (OXI-Cliq, Nellcor, Boulder, CO, USA) placed on the left hind limb.

The 20 animals were randomly assigned to the following groups: sham group (n=5), sham operation, no treatment; control group (n=5), no procedure before euthanasia; SAH group (n=5), SAH induction, no treatment; HBOT group (n=5), SAH induction, and received five sessions of HBOT at 2.4 atmospheres absolute (ATA) for 2 hours. HBOT started 12 h after SAH induction and was given twice daily for the first two days and once on the third day. Experimental trials were performed by four investigators who were not blinded to the groups.

Induction of experimental SAH and sham operation

The local hair on the neck was shaved, and the skin was sterilized with 75% ethanol. A midline occipita-cervical incision was made, and suboccipital muscles were dissected to expose the atlanta-occipital membrane. The membrane was punctured using a 23-gauge needle to withdraw cerebrospinal fluid (CSF) from the cisterna magna. The procedure was finalized with reinjection of withdrawn CSF into the cisterna magna in the sham group (sham operation). Autologous non-heparinized blood (0.9 mL) obtained from the femoral artery was slowly injected into the cisterna magna in the SAH and treatment groups over 20 seconds (SAH induction). Each rabbit was then placed in a head-down position (30° angle for 30 min). After recovery from the anesthesia, the rabbits were returned to the cages.

Perfusion-fixation

At 72 h post-injection, the animals were anesthetized and monitored as described. The rabbits in all groups were euthanized by perfusion and fixation. After the thorax was opened, a cannula was placed in the left ventricle, the descending thoracic aorta was clamped, and the right atrium was opened. After perfusion with Hanks balanced salt solution as a flushing solution (Sigma Chemical Co.), pH 7.4 at 37°C, 1500 mL, a fixative was perfused (2% paraformaldehyde, 2.5% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4 at 37°C, 1000 mL). Perfusion was performed using a perfusion pump at a standard pressure of 0.1 Bar. En bloc removal of the brain, liver, and ileum was carried out on each animal, and these materials were stored in a fixative solution at 4°C overnight.

Morphometric analysis of brain, liver, and ileum

Brain sections were embedded in paraffin and sections cut at a thickness of 0.5 ?m, mounted onto glass slides, and stained with

hematoxylin-eosin to be investigated under a light microscope. Each section was digitally photographed at 10× and 20× magnifications to show subarachnoid hemorrhage.

Liver and ileum specimens were fixed in 10% formalin and embedded in paraffin. For morphologic examination, 4-?m?thick paraffin sections were deparaffinized with xylene, stained with hematoxylin and eosin, and Masson"s trichrome, and examined under a BX53 microscope (Olympus, Tokyo, Japan).

The histologic analyses investigated the liver and ileum for edema and inflammation. These were graded as absent (0), mild to moderate (1) or severe (2).

To quantitate arteriolar diameter of liver and ileum tissues, we used image analysis software (Cellsens Entry 1.6, Olympus Corp., Tokyo, Japan). The cross-sectional diameters were measured at ten high power fields in each slide. The shortest diameter was selected when the cross section of the arteriole was elliptical in shape.

Statistical analysis

Statistical comparisons for arteriole diameters, inflammation and edema between the groups of each different organ were performed using GraphPad Prism 5 (Graph Pad Software Inc., San Diego, California, USA) and the Mann-Whitney U test. Group graphs are also illustrated by using the same program and mean ± SEM values. Significance was set at $p< 0.05$.

RESULTS

Confirmation of SAH

A subarachnoid clot adjacent to basilar artery was observed in all histopathologic views obtained from animals subjected to SAH (Figure 1).

Physiologic parameters

In the course of the surgical procedure, continuous monitoring of MAP and blood gas results showed no significant differences between the groups ($p> 0.05$). The mean ± SD MAP and blood gas results for the groups are shown in Table 1.

Evaluation of tissue edema

According to the histologic analysis, there was a prominent edema formation in the liver and ileum tissues in the SAH and HBOT groups compared with the control and sham groups, but this was not significant (Table 2). Figure 2 and 3 shows some representative photos of the histologic changes in the liver and ileum tissues.

Evaluation of tissue inflammation

The degree of inflammation was significantly greater in the SAH group compared with the control and sham groups ($p= 0.035$, $p=0.046$, respectively) for liver tissue. In the SAH group, inflammation was significantly increased in the ileum tissue compared with the sham and control groups ($p=0.048$, respectively). Inflammation in the SAH group was higher compared with the HBOT group, but this was not significant. No difference was found between the sham and control groups in terms of inflammation ($p>0.05$) (Table 3) (Figure 4, 5).

Analysis of arteriolar diameter of liver and ileum tissue

The mean cross-sectional arteriolar diameter for the liver were 12.97 ± 1.12 mm in the control group, 14.33 ± 1.07 mm in the sham group, 12.84 ± 0.63 mm in the SAH group, and 17.51 ± 1.53 mm in the treatment group. The mean cross-sectional diameter of arteriol in the liver was significantly increased in the HBOT group compared with the SAH group ($P = . 0.022$). Other results did not differ among the groups for liver tissues ($P > 0.05$). The arteriolar diameter for ileum were 10.6 ± 0.33 in the control group, 11.96 ± 1.04 in the sham group, 12.75 ± 0.65 in the SAH group, and 11.13 ± 0.95 in the HBOT group. No significant differences were detected among the groups for ileum tissues (Table 4, Figure 6).

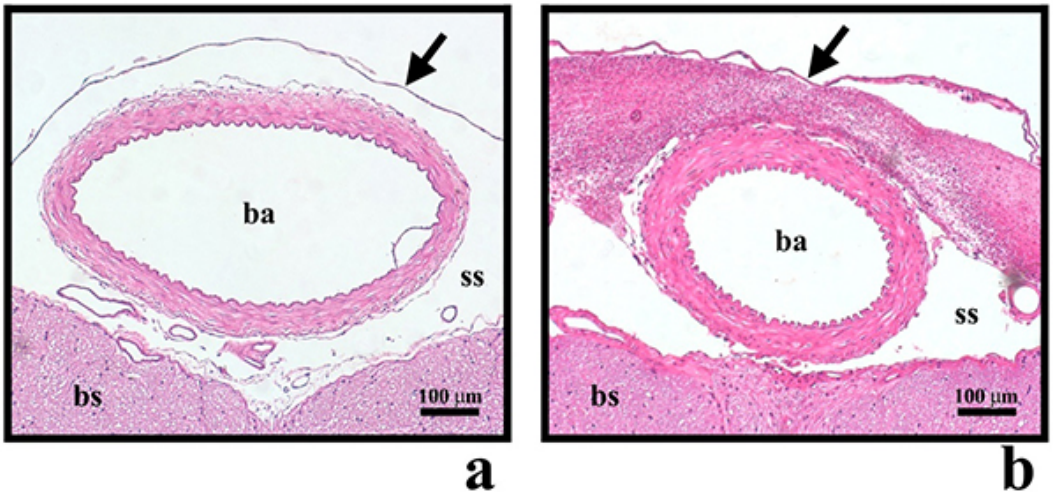

Figure 1: *Photographs of cross-section samples from control and subarachnoid hemorrhage group at 10× magnification (arrows showing arachnoid membrane, ba: basillar artery, bs: brainstem, and ss: subarachnoid space).*
a) Cross-section sample from the control group
b) Cross-section sample from the SAH group showing significant hemorrhage in subarachnoid space

Table 1. The mean ± SD of MAP and blood gas results for the groups.

GROUP	MAP (mmHg)	pH(mmHg)	pCO_2(mmHg)	pO_2	sPO_2
SHAM	77.10±6.15	7.455±0.075	36.2±4.4	80.6±6.90	96.50±0.1
CONTROL	78.40±7.20	7.444±0.O50	34.7±3.8	85.2±7.88	96.80±0.2
SAH	77.50±6.45	7.448±0.060	35.10±4.1	84.6±8.26	95.7±0.1
HBOT	78.15±6.70	7.452±0.070	36.1±4.0	87.0±12.10	97.00±0.3

Table 2. Comparisons of of tissue edema in liver and ileum

EDEMA	LIVER (mean ± SEM)*	ILEUM (mean±SEM)*
SAH	1.2 ± 0.2	2.03 ± 0.03
HBOT	1.6 ± 0.25	1.8 ± 0.2
SHAM	1.2 ± 0.2	2.25 ± 0.25
CONTROL	1.2 ± 0.2	1.5 ± 0.5

*The percentage of edema cells expressed as mean ± SEM of 10 fields

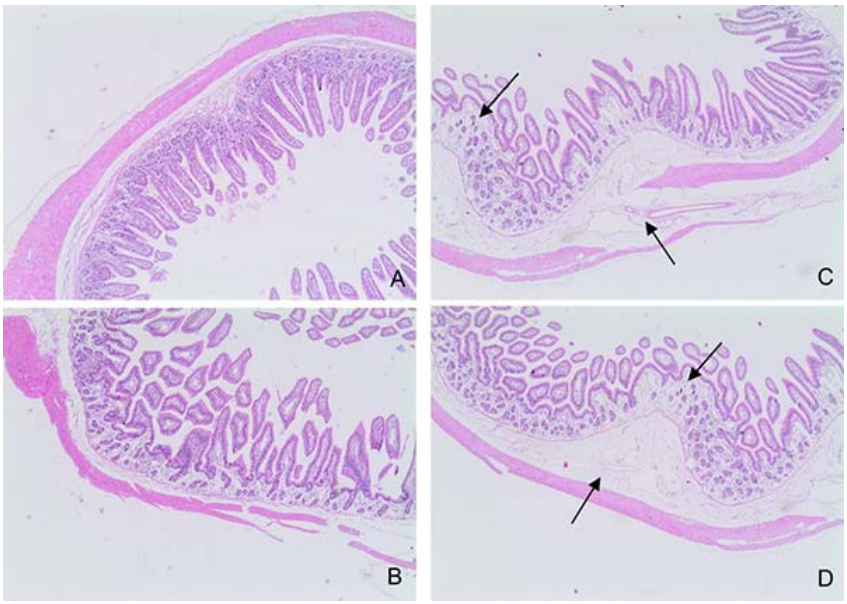

Figure 2: *Photographs of cross-section samples of ileum tissues from each group at 40 × magnification (arrows showing edema formation). (A) Cross-section sample from the SHAM group. (B) Cross-section sample from the control group. (C) Cross-section sample from SAH group showing prominent edema. (D) Cross-section sample from the HBOT group showing prominent edema not decreasing with treatment after SAH.*

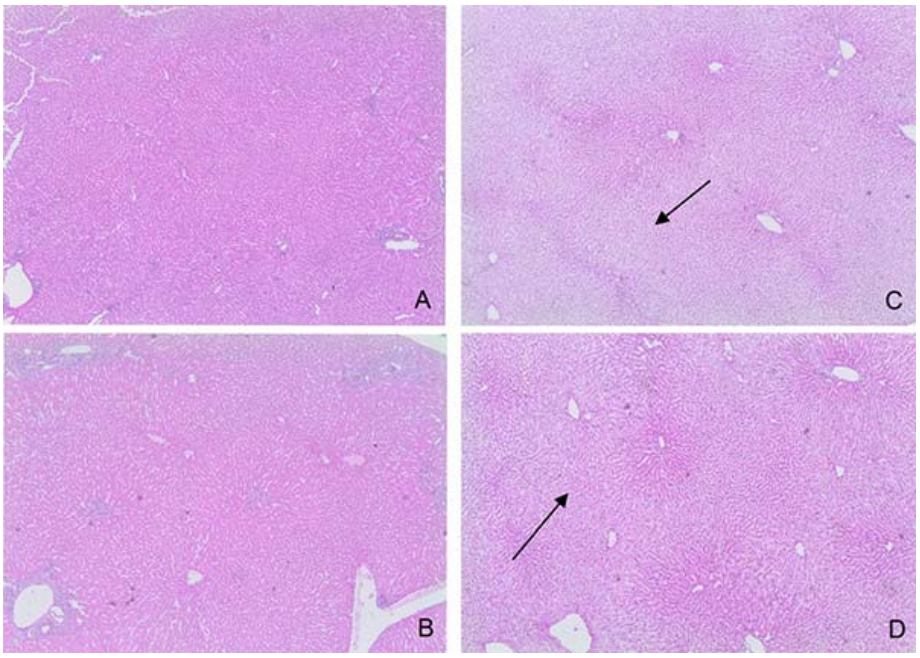

Figure 3: *Photographs of cross-section samples of liver tissues from each group at 40 × magnification (arrows showing edema formation). (A) Cross-section sample from the SHAM group with no edema. (B) Cross-section sample from the control group with no edema. (C) Cross-section sample from the SAH group showing prominent edema seen as lighter areas. (D) Cross-section sample from the HBOT group showing prominent edema seen as lighter areas, which was not decreasing with treatment after SAH.*

Table 3. Comparisons of tissue inflammation in liver and ileum

INFLAMMATION	LIVER (mean ± SEM)*	ILEUM (mean±SEM)*
SAH	***. ## 1.6 ± 0.24	**1.5 ± 2.9
HBOT	1 ± 0.32	1 ± 0.32
SHAM	*** 1.02 ± 0.02	** 0.5 ± 0.29
CONTROL	## 0.8 ± 0.2	**0.5 ± 0.29

*The percentage of inflammatory cells expressed as mean ± SEM of 10 fields. *** p=0.046. ## p=0.035 ** p= 0.040

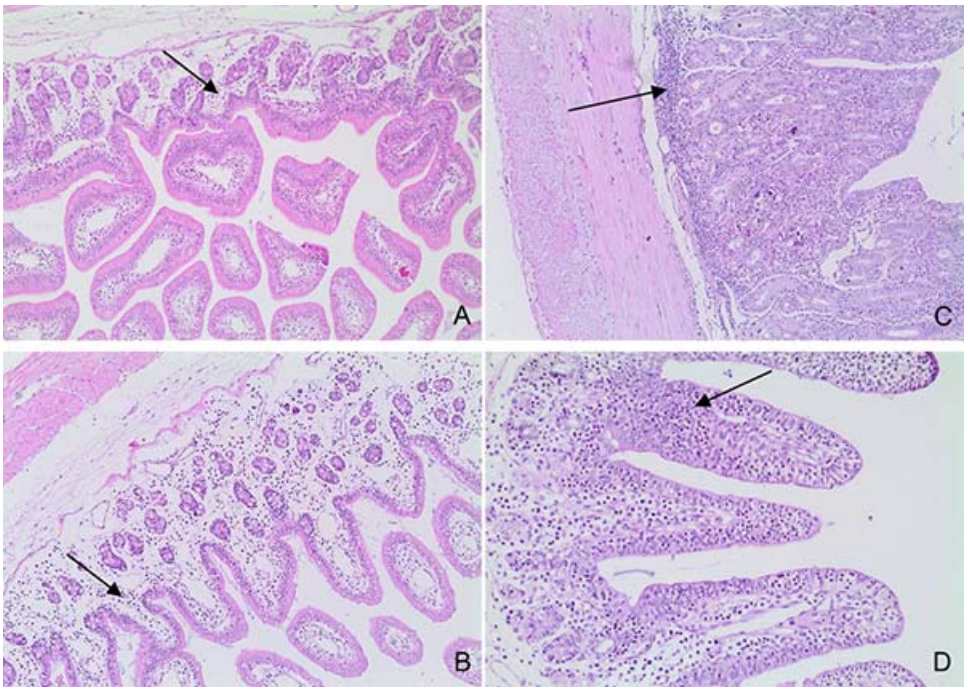

Figure 4: *Photographs of cross-section samples of ileum tissues from each group at 100 × magnification (arrows showing inflammatory cells). (A) Cross-section sample from the SHAM group with a few scattered inflammatory cells in the lamina propria. (B) Cross-section sample from control group with minimal inflammatory cells. (C) Cross-section sample from the SAH group showing dense inflammation. (D) Cross-section sample from the HBOT group showing dense inflammation pattern, which was not reducing with treatment after SAH.*

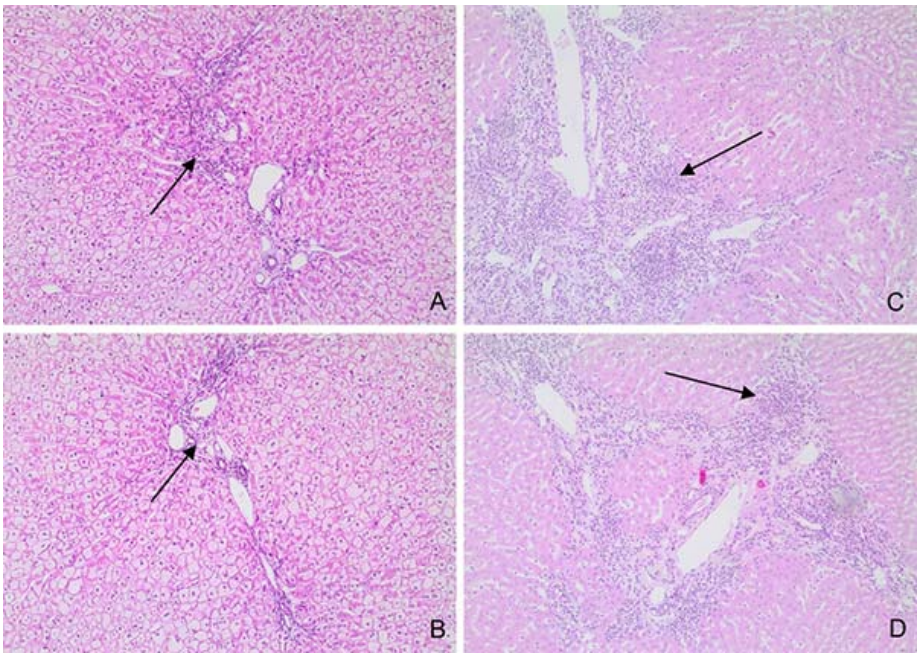

Figure 5: *Photographs of cross-section samples of liver from each group at 100 × magnification (arrows showing inflammatory cells in portal areas). (A) Cross-section sample from the SHAM group with minimal inflammatory cells. (B) Cross-section sample from the control group with a few inflammatory cells. (C) Cross-section sample from the SAH group showing dense inflammation. (D) Cross-section sample from the HBOT group showing dense inflammation pattern, which was not reducing with treatment after SAH.*

Table 4: To quantitate arteriolar diameters of liver and ileum

	ARTERIOLE DIAMETERS (mean ± SEM)			
	SAH	HBOT	SHAM	CONTROL
LIVER	12.84 ± 0.63 *	17.51 ± 1.53*	14.33 ± 1.07	12.97 ± 1.12
ILEUM	12.75 ± 0.65	11.13 ± 0.95	11.96 ± 1.04	10.6 ± 0.33

Values are the mean ± SEM of independent determinations using arteriolar diameters from different animals (n=5).* p=0.022

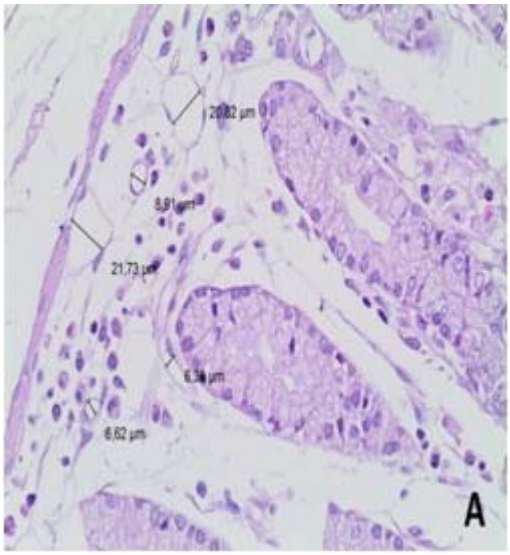

Figure 6. *Photographs of the cross-sectional arteriolar dimention from ileum (A) and liver (B) at 400 × magnification.*

DISCUSSION

Our study investigated the effect of HBOT on SAH-induced histopathologic changes in the gastrointestinal system. The main findings of this study are; 1) inflammatory cell accumulation occurred in liver and ileum tissues after SAH, 2) SAH-induced inflammation was not attenuated by HBOT. These results indicate that HBOT has no beneficial effect on the regression of hepatic and ileum inflammation after SAH.

SAH decreases cerebral blood flow, and causes global brain ischemia and global oxidative stres (13,14). Inflammatory reactions play a critical role in the pathophysiology of tissue repair after injury insult. Subarachnoid hemorrhage contributes to brain damage by an inflammatory-mediated cascade. It has been demonstrated that SAH increases expression of inflammatory mediators (15). Ischemic injury and inflammation account for vasospasm progression (16). Vasospasm aggravates neurogenic injury and impairs brain oxygenation, which leads to high morbidity and mortality in SAH (17). In recent years, it was reported that vasospasm development was multifactorial, thus many experimental studies were conducted regarding treatment of histopathologic, biochemical, and morphometric aspects of vasospasm in subarachnoid hemorrhage (18-21).

An experimental study demonstrated that SAH could induce intestinal cytokine overproduction and marked damage of intestinal mucosa structure was shown through altered intestinal mucosa morphology. Nuclear factor-B (NFB) binding activity was significantly increased in the SAH group (8). A recent study also showed up-regulated tissue edema and inflammatory response after SAH, which was represented by inflammatory cell infiltration and inflammatory cytokines activation (22). As in these studies, there was increased inflammation in the intestine in our study.

Chemokines are markedly induced by acute inflammatory lesions to the central nervous system. A focal injury to the brain generates a rapid hepatic response, despite the presence of an intact blood-brain barrier (23). Chemokine expression by the liver results in neutrophil recruitment to the liver and consequent hepatocellular damage (24). This phenomenon may contribute to organ dysfunction, which is often observed after acute brain injury (23). A study using NFB reporter mice revealed that the principal organ driving the inflammatory response after injury to the CNS was the liver (25). In parallel, our study also demonstrated inflammatory cell accumulation in liver tissues.

There are several studies that support the role of HBOT in protecting cells against I/R injury (26,27). HBOT-induced neuroprotection after SAH includes increased oxygen concentration in tissues, regulation of inflammatory processes, apoptosis inhibition, increased antioxidant molecules, improved neutrophil action and cerebral metabolism (28). HBOT attenuates cerebral vasospasm through its anti-inflammatory properties (29,30). It is also useful for heat-induced activated inflammation, ischemic, and oxidative damage in brain regions (31). It also has a therapeutic effect after ischemic injury of the liver and small intestine. However, the detailed molecular mechanism of this action is still unknown (30).

An experimental study demonstrated that HBOT preconditioning had a protective effect on liver exposed to ischemia and reperfusion (32,33). The effectiveness of this treatment for the liver was related to its antiapoptotic activity (34). In contrast, Lima et al. showed that preconditioning with HBOT aggravated hepatocellular injury (35). In another preconditioned experimental model, I/R injury of skin flap grafts was diminished using HBOT (30).

Bertoletto et al. showed that HBOT had an antiapoptotic effect on rat intestinal mucosa after an I/R injury model (36). It was suggested that HBOT had a protective effect on the small intestine in ischemia-reperfusion injury (27,37). In our study, the SAH-induced inflammation was not ameliorated after HBOT.

The major limitation of our study is that the inflammation was determined only through histologic analysis with light microscopy. An immunohistochemical assay for levels of inflammatory cytokines in hepatic and ileum tissues could be studied before and after HBOT. Future studies should address the effectiveness of HBOT on the levels of gastrointestinal and hepatic inflammatory cytokines and NFB binding activity as the potential pathway of inflammation.

CONCLUSION

Based on the results of the current study, SAH prompted inflammation in the gastrointestinal system. We showed that HBOT (five sessions, each for two hours performed 12 hours after SAH induction) was ineffective in the attenuation of inflammation in liver and ileum tissues after SAH.

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CONFLICT OF INTEREST: None

Correspondence to:
Fethi Gul
E-mail: gulfethi@gmail.com

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