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Does intraabdominal use of Ankaferd Blood Stopper cause increased intraperitoneal adhesions?

Ankaferd Blood Stopper'in karın içi kullanımı periton içi yapışıklık oluşumunu arttırır mı?

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BACKGROUND

The aim of this study was to investigate whether intraabdominal Ankaferd Blood Stopper (ABS) causes increased intraabdominal adhesion formation and to determine any side effects of ABS *in vivo*.

METHODS

The present experimental study was designed to examine the effects of Ankaferd solution on peritoneal adhesion formation in a rat model of cecal abrasion. Intraperitoneal adhesions were assessed macroscopically and histopathologically on the 10th postoperative day. The possible adverse affects of ABS on liver and lung tissues were analyzed histopathologically, and blood chemistry was also evaluated.

RESULTS

Our study revealed that ABS reduced intraperitoneal adhesion formation in an experimental rat model. The blood chemistry was not disturbed due to ABS administration. Intraperitoneal administration of ABS led to some minor changes in the lungs and serosal surfaces of the intestines, with minor architectural changes in the liver that were not considered as toxic. Further studies with various application doses and routes with more detailed cellular analysis are thus warranted to clarify the possible pleiotropic and adverse effects of this new agent away from hemostasis.

CONCLUSION

There was less intraperitoneal adhesion formation in the ABS group than in the control group and saline group. Intraperitoneal administration of ABS has no toxic effects on blood chemistry or the lungs, kidneys and the liver, but it has some minor adverse effects.

Key Words: Adhesion; Ankaferd Blood Stopper; hemostasis; rat; side effect.

AMAÇ

Bu çalışmanın amacı, karın içi kullanılan Ankaferd Blood Stopper'in (ABS) periton içi yapışıklık oluşumunu arttırıp arttırmadığını ve *in vivo* kullanıma bağlı majör toksik etkilerini irdelemektir.

GEREÇ VE YÖNTEM

Bu deneysel çalışma, çekal abrazyon uygulanan sıçan modelinde Ankaferd solüsyonunun periton içi yapışıklık oluşumu üzerine etkisini değerlendirmek üzere dizayn edildi. Periton içi yapışıklıklar cerrahi uygulama sonrası 10. gün makroskopik ve histopatolojik inceleme ile belirlendi. Yan etki varlığını irdelemek için kan, akciğer ve karaciğer dokuları alındı.

BULGULAR

Ankaferd Blood Stopper'in kullanımı ile karın içi yapışıklık oluşumunun azaldığı görüldü. ABS uygulanmasının kan biyokimyasal incelemelerinde herhangi bir bozulmaya neden olmadığı saptandı. Ancak akciğerlerde ve bağırsakların serozal yüzeylerinde akut ve kronik enflamatuvar değişiklikler ve karaciğerde minör yapısal değişiklikler izlendi. Bu değişikliklerin hiçbiri toksik değişiklik olarak değerlendirilmedi. ABS'nin diğer etkilerinin belirlenmesi için farklı dozlarda ve farklı klinik senaryolarda ileri çalışmalara ihtiyaç vardır.

SONUÇ

Periton içi yapışıklık oluşumu ABS uygulanan grupta kontrol grubu ve SF grubuna kıyasla daha az görüldü. İntraperitoneal ABS kullanıma bağlı olarak herhangi bir toksik etki saptanmamakla birlikte bazı minör değişiklikler gözlenmiştir.

Anahtar Sözcükler: Adezyon; Ankaferd Blood Stopper; hemostaz; sıçan; toksik etki.

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Postoperative adhesion formation occurs at a very high frequency after abdominal surgery.[1-3] Most cause no serious sequelae; however, some adhesion-related problems, such as intestinal obstruction,[4] chronic abdominal pain,[5] infertility, increased cost, and increased rate of complications associated with subsequent operations,[6,7] emerge in around one-third of the patients.[8,9]

Hemorrhage remains one of the major causes of mortality following trauma, and is also a significant concern during major surgical interventions. Ankaferd Blood Stopper® (ABS) (Trend Teknoloji İlaç AS, Istanbul, Turkey) is a folkloric medicinal plant extract. It has been approved in the management of external hemorrhage and dental surgery by the Ministry of Health in Turkey.

Our previous study revealed that ABS is an effective hemostatic agent for controlling hemorrhage from liver laceration.[10] ABS leads a protein network formation that contains aggregation of blood cells, particularly erythrocytes, and interactions between ABS and blood proteins, mainly fibrinogen.[11] Tests have stated its safety, efficacy, sterility, and non-toxicity for external usage (www.ankaferd.com). Nevertheless, the safety and non-toxicity of ABS for intraperitoneal usage and the effects of ABS on peritoneal adhesion have yet to be addressed.

Prevention of peritoneal adhesions has become one of the most studied issues in surgery. Numerous agents, such as phospholipase inhibitors, dextran, corticosteroids, phospholipids, methylene blue, anti-inflammatory drugs, polysaccharides, bioresorbable membranes, and tissue plasminogen activator, have been investigated in the prevention of adhesions.[12-17] Unfortunately, an effective solution to prevent peritoneal adhesion formation has not been achieved to date.

The present experimental study was designed to investigate whether intraabdominally administered Ankaferd causes increased intraabdominal adhesions in comparison with saline solution in a rat model of cecal abrasion. The possible adverse affects of ABS on the liver and lung tissues were also analyzed together with blood chemistry.

MATERIALS AND METHODS

Twenty-five Wistar albino rats, housed in a climate-controlled facility, were used in this study. Objects were fed with pellet food, produced specifically for experimental animals, and allowed food and water ad libitum. All animals were maintained in Zonguldak Karaelmas University (ZKU) Experimental Animals Research Unit. The study protocol was approved by the Ethics Committee of our institution and experiments were conducted according to guiding principles for the care and use of laboratory animals.

Rats were given water until 12 hours before surgery. Strict sterile surgical protocols were maintained throughout the experimental period. The animals were weighed and anesthetized with intramuscular injection of 100 mg/kg ketamine (Ketalar, Parke Davis-Eczacıbaşı, Istanbul, Turkey). Animals were assigned to one of three groups (control group, saline group, and ABS group) randomly. The mean weight of the three groups was comparable. The midline of the abdomen where the incision was made was shaved and antisepsis was provided with povidone iodine. Non-powdered gloves were used for the experiment. After performing a 3 cm midline laparotomy, the antimesenteric border of the cecum was abraded with dry sterile gauze, rubbing approximately 20 times, until punctuate bleeding occurred on about a 2 cm area. A similar area of the adjacent side-wall peritoneum was abraded in the same fashion. The above-mentioned procedure was performed to all test subjects by the same surgeon in a similar manner. The viscera were replaced. No medication was administered to the control group. Rats in the saline group were given 3 ml of intraperitoneal saline solution, and rats in the ABS group were given 3 ml of ABS solution, after 1:3 dilutions with saline, intraperitoneally. The wound was closed with two layers of running suture. Rats were sacrificed on postoperative day 10 by means of blood withdrawal via cardiac puncture, under ketamine anesthesia.

Macroscopic Evaluation

A reversed U-shaped incision was made in order to view the entire adhesions and to perform an accurate adhesion grading. The presence of pericecal adhesions was assessed and graded as 0, 1, 2, 3, compatible with the Evans model[18] for each rat (Table 1). The evaluation of adhesions was performed by one of the investigators (GKC) blind to the study groups and the exact procedure of the experiment.

Table 1. Adhesion severity score - Evans model

Adhesion grade	Definition
0	No adhesion
1	Filmy and avascular adhesions separating spontaneously
2	Firm and limited vascular adhesions separated by traction
3	Dense adhesions separating by sharp dissection

The terminal ileum and cecum were excised en-bloc without separating adhesions for histological evaluations. In order to investigate possible systemic toxicities and adverse effects, blood samples together with liver and lung tissues were also collected.

Microscopic Evaluation

Tissue specimens from the terminal ileum-cecum, lung and liver were fixed in 10% neutral formalin solution and embedded in paraffin. Sections were cut with a cryostat at 4-5 μm thickness from the paraffin blocks of each tissue. Specimens were then deparaffinized and stained with hematoxylin-eosin (H-E) or Perls' Prussian blue, a histochemical method for hemosiderin pigments. A light microscope was used for evaluation. The presence of adhesions and intensity of inflammation around the terminal ileum-cecum were detected histopathologically. H-E sections of the lung were evaluated for the presence of congestion, acute and chronic inflammatory reaction, hemosiderin-laden macrophages, interstitial emphysematous changes, and alveolar macrophages histopathologically. These H-E sections of the liver were evaluated for congestion, sinusoidal dilatation, steatosis, spotty necrosis, portal tract inflammation, hepatocyte degeneration, presence of hemosiderin-laden macrophages, and thickening of the liver capsule histopathologically. The presence of these findings were detected during microscopic evaluation of H-E cross-sections histopathologically and graded on a scale ranging from 0 (absence of the characteristic) to 3 (intense presence of the same features). Perls' Prussian blue sections were evaluated to detect the presence of hemosiderin pigments. All tissue sections collected for light microscopy were examined by the same pathologist without knowledge of the experimental groups.

Blood Chemistry

Blood samples were centrifuged and the resulting supernatant was collected and then sent to the biochemistry laboratory. Blood samples were evaluated immediately for biochemical parameters. The level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), and creatinine were determined.

Statistical Analysis

Values are expressed as mean ± SD. Univariate analysis of variance test was used to compare differences between the saline-treated group, ABS-treated group and control group. The criterion for significance was accepted as $p<0.05$. Independent samples t test was used to compare blood chemistry results for saline and ABS groups. Likelihood ratio (LR) and chi-square test were used for comparison of histopathological analysis.

RESULTS

Analysis of the adhesions scores according to the Evans model and histopathologic examination designated significant differences between the groups. The presented data demonstrated that the intraperitoneal administration of ABS solution can reduce intraperitoneal adhesion ($p=0.015$). The mean adhesion scores in the control group, saline group and ABS group were 3.43±0.79; 2.44±1.01 and 2.11±0.93, respectively. We observed that saline decreased intraperitoneal adhesion formation in comparison with the sham-treated group ($p=0.057$). While adhesion scores tended to be lower in the ABS group than the saline group, the difference was not significant ($p=0.465$). On the other hand, adhesion score in the ABS group was significantly diminished when compared with the control group ($p=0.015$). Adhesion scores obtained from Evan's model are presented in Table 2.

Histopathological analysis revealed no significant difference in terms of mucosal and submucosal inflammation between the three groups ($p=0.154$). Conversely, the severity of serosal inflammation was increased in the ABS group, when compared to the other two groups ($p=0.040$). Histopathological examination results are presented in Table 3.

In the ABS group, histopathologic examination of ileal and cecal sections demonstrated a reduced adhesion formation on the serosal surfaces. The presence of hemosiderin pigments on serosal surfaces by Perls' Prussian blue and intense inflammatory cell reaction that was a response to hemosiderin pigment accumulation were also detected in the ABS group sections (Fig. 1).

Histopathological examination of the lung speci-

Table 2. Macroscopic evaluation of adhesion scores according to the Evans model

Groups	Adhesion score				
	0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)
Control group (n:7)	0 (0)	0 (0)	1 (14.3)	2 (28.6)	4 (57.1)
Saline group (n:9)	0 (0)	1 (11.1)	5 (55.6)	1 (11.1)	2 (22.2)
ABS group (n:9)	0 (0)	2 (22.2)	5 (55.6)	1 (11.1)	1 (11.1)

Table 3. Histopathologic findings of tissue specimens from the terminal ileum-cecum*

Score	Control group (n:7)				Saline-treated group (n:9)				ABS-treated Group (n:9)			
	0	1	2	3	0	1	2	3	0	1	2	3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mucosal inflammation	7 (100)	0	0	0	3 (33.3)	4 (44.4)	2 (22.2)	0	5 (55.6)	4 (44.4)	0	0
Submucosal inflammation	5 (71.4)	2 (28.6)	0	0	2 (22.2)	3 (33.3)	3 (33.3)	1 (11.1)	2 (22.2)	5 (55.6)	2 (22.2)	0
Serosal inflammation	1 (14.3)	5 (71.4)	1 (14.3)	0	2 (22.2)	2 (22.2)	3 (33.3)	2 (22.2)	1 (11.1)	2 (22.2)	3 (33.3)	3 (33.3)
Fat necrosis	7 (100)	0	0	0	4 (44.4)	4 (44.4)	1 (11.1)	0	6 (66.7)	0	3 (33.3)	0
Hemosiderin-laden macrophages	7 (100)	0	0	0	5 (55.6)	2 (22.2)	2 (22.2)	0	0	3 (33.3)	4 (44.4)	2 (22.2)
Adhesion	0	7 (100)	0	0	5 (55.6)	4 (44.4)	0	0	6 (66.7)	3 (33.3)	0	0

*Histopathologic findings were scored as follows: none: 0, weak: 1, moderate: 2, and intense: 3, and absence of adhesion: 0, and presence of adhesion: 1.

mens revealed that pulmonary congestion was similar between the three groups. The ABS group had severe chronic inflammation compared to the saline and control groups (LR: 0.002). Acute inflammation was more prominent in the ABS group than the other two groups (LR <0.001) (Fig. 2). There were no differences between groups in terms of emphysematous development and the presence of alveolar macrophages (LR: 0.295 and 0.182, respectively).

Histopathological analysis of the liver specimens revealed no significant differences between groups in terms of hepatic congestion, inflammation of the portal tract, spotty necrosis, and fluid accumulation (LR: 0.295, 0.225, 0.673 and 0.120, respectively). The ABS group had more dilatations of the sinusoids and thicker liver capsule than the other two groups (LR: 0.003 and <0.0001, respectively). The histopathological evaluation of the liver specimens, which were grossly mat and yellow-brown in appearance, revealed that there were old hemorrhagic foci characterized by the presence of hemosiderin-laden macrophages lying into the portal spaces from the capsule. Multinuclear giant cells consisting of occasional foreign substances and fibrin-like material were also observed. Microscopic evaluation revealed no evident findings of degeneration or inflammation in hepatocytes (Fig. 3).

No statistically significant difference was detected between the saline and ABS groups in terms of AST, ALT, and ALP values on blood chemistry analysis. BUN values were lower in the ABS group than in the saline group and control group (p=0.037 and p=0.049, respectively). On the other hand, creatinine values were similar between the three study groups.

DISCUSSION

Adhesions after abdominal trauma are abnormal attachments between tissues and organs. The formation of adhesion might result from mechanical peritoneal damage, tissue ischemia and the presence of foreign materials.[1] Adhesion formation occurs as a consequence of the normal physiological wound healing process following trauma to the peritoneal surfaces.[4] Peritoneal adhesions that impair the integrity of the peritoneum almost always develop within 5-7 days following trauma.[19] The optimal time for quantification of adhesions in rats is 7 or more days after operation.[20] Therefore, adhesion formation in the present study was evaluated after 10 days.

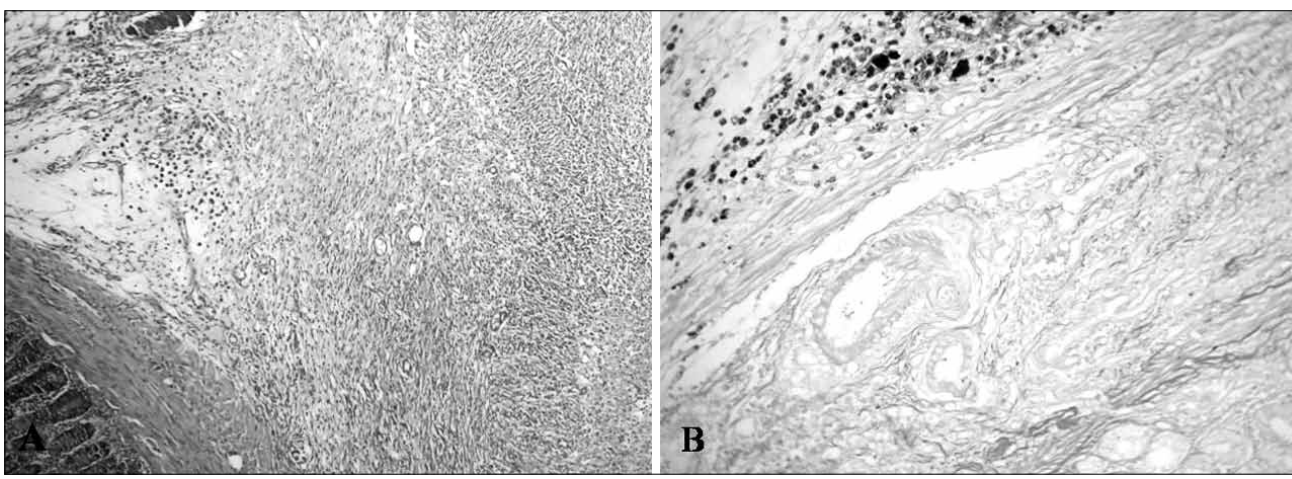

Fig. 1. The microscopy of ileum-cecum sections of the ABS group. **(A)** Fibrinous exudates, serosal thickening, edema, inflammatory cell reaction, micro abscess focus, and granulation tissue formation in the serosal surfaces (H-E x 100). **(B)** Accumulation of hemosiderin pigments dispersed in serosal surfaces (Perls' Prussian blue, x 200).

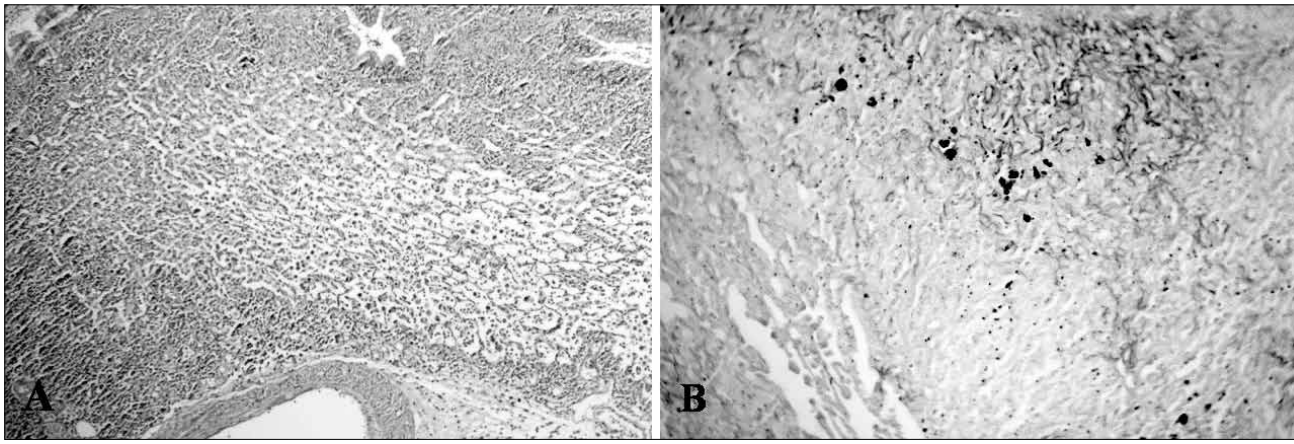

Fig. 2. The microscopy of lung sections of the ABS group. **(A)** Edema, haphazardly scattered interstitial inflammatory infiltration, patchy appearance of neutrophil accumulation, alveolar cell hyperplasia (H-E x 100). **(B)** Presence of sparse and focal hemosiderin pigments in interstitial field (Perls' Prussian blue, x 200).

The effect of ABS, which seems to be an effective hemostatic agent, on intraperitoneal adhesion formation has not been investigated thus far. The present study evaluated the effect of ABS on intraperitoneal adhesions, and also aimed to clarify the possible side effects on the liver, lungs and blood chemistry.

Several scoring models have been proposed to grade adhesions in experimental studies.[18,21,22] The Evans model, which is a well-defined and similar method, was used for grading adhesions in the present study. Evan's model[18] grades adhesions according to the adhesion intensity to sero-serous surfaces. The intensity of the adhesions plays a significant role in the development of complications due to peritoneal adhesions. Clinical judgement of adhesions according to the Evan's model showed significantly reduced adhesions in the ABS group when compared with the control group.

The effect of saline on adhesion formation is controversial. Some investigators[23,24] found no influence of saline on peritoneal adhesion formation, whereas an anti-adhesive effect was reported in several studies.[25,26] On the contrary, van Westreenen et al.[27] suggested increased adhesion formation with perioperative lavage. In our study, saline administration decreased intraperitoneal adhesion formation in comparison with sham-treated group. Adhesion scores tended to be lower in the ABS group than in the saline group; however, the difference was not significant. According to the data of the present study, the adhesion protection effect of ABS is slightly more potent than that of saline. Consistently, it is reasonable to hypothesize that ABS itself does not cause adhesion formation. Moreover, intraperitoneal administration reduces adhesion formation to some extent, in contrast to the increased serosal inflammation in the ABS group. There are certain mechanisms described in prevention of the adhesion formation.[12,17,28-30] The cellular and biochemical mechanisms by which ABS reduces adhesion formation should be investigated in further

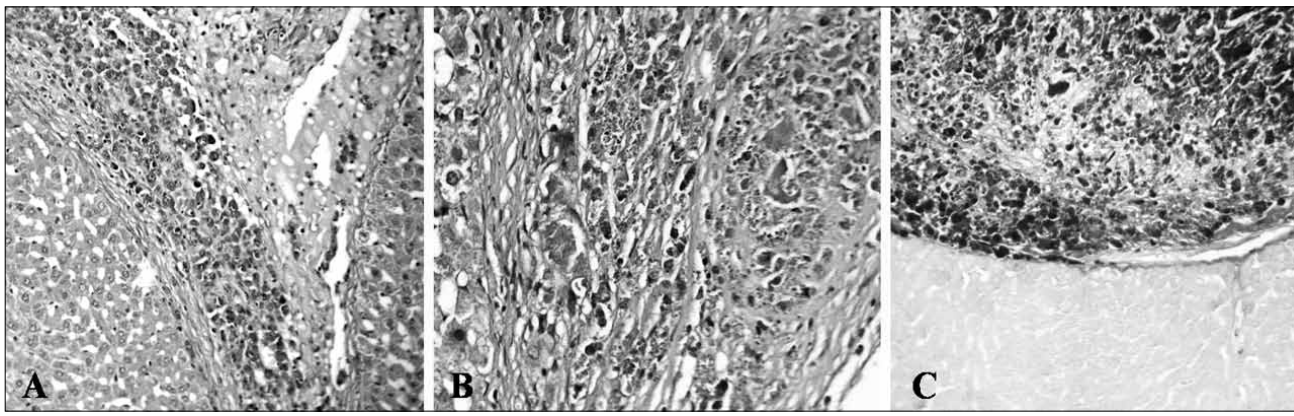

Fig. 3. The microscopy of liver sections of the ABS group. **(A)** Old hemorrhagic foci characterized by the presence of hemosiderin-laden macrophages lying into the portal spaces from the capsule and scattered haphazardly in the capsule (H-E x 200). **(B)** The presence of fibrin-like material with hemosiderin-laden macrophages forming clusters in the capsule (H-E x 400). **(C)** Accumulation of hemosiderin pigments in the liver capsule (Perls' Prussian blue, x 200).

studies. Although the adhesion scoring was performed by an investigator blind to the groups and the exact procedure of the study, a lack of repeated scoring limits determining intra- and inter-observer bias, which lowers the consistency of the scoring method.

Another limitation of the present study is the dosage of the agent administered intraperitoneally. The concentrations[17,31] and viscosities[32] of the substances used to prevent adhesion formation are important parameters in prevention of adhesions. ABS solution diluted 1:3 with sterile 0.9% NaCl solution was used in the present study.

Serosal inflammation in the ABS group might be a result of protein network formation due to the interactions of ABS with minor hemorrhage and punctate bleeding areas on serosal surfaces that occurred during laparotomy. Inflammation of the serosal surfaces is one of the major causes of adhesions. Surprisingly, the present data demonstrates that increased serosal inflammation of the intestines is not gradually associated with severe adhesions. The mechanisms of decreased adhesions in the milieu of increased inflammation are not clear. This might be attributed to the formation of a protein network resulting from the interaction of ABS and the blood revealed during the experimental process.

Another aspect of the present study was to investigate the possible side or toxic effects of intraperitoneally administered ABS on the liver, lung and kidney tissues. The comparisons between the groups were performed by means of biochemical analysis, including liver and renal function tests, together with histopathological evaluation, to clarify the effects of ABS solution on the liver or lung tissue on a cellular basis. BUN values were found to be significantly lower in the ABS group than in the saline group. Nevertheless, creatinine values were determined to be similar between the groups. Accordingly, it is reasonable to conclude that, away from exerting an adverse effect, ABS administration might improve renal functions to some extent.

The comparison in terms of liver function tests revealed no statistically significant difference between the saline and ABS groups. Histopathological evaluation of the liver specimens demonstrated a significant capsule thickening with more sinusoidal dilatation and hemosiderin-laden macrophages in the ABS group, when compared to control and saline group animals. Liver capsule thickening in the ABS group may be related to the increased formation and removal of the protein network developed secondary to the ABS application. In accordance with the above-mentioned data, minor effects of ABS application on liver architecture are something accurate; however, these should not be considered as toxic.

Histopathological evaluation of the lung specimens revealed neither emphysematous development nor presence of alveolar macrophages in any of the study groups. Acute and chronic inflammatory changes were determined to be significantly severe in the ABS group when compared to the saline and control groups. Since the principal aim of the present study was to clarify the effects of ABS on intraabdominal adhesion formation and its possible adverse effects on the liver, lung and blood chemistry, the cellular mechanism responsible for any side effect was beyond the scope of this experimental study. The underlying reasons and cellular pathways accounting for the increased acute and chronic inflammation observed in ABS group should be investigated by means of further studies with detailed technical and biological modalities.

In conclusion, the results of the present experimental study revealed that intraperitoneal ABS application did not lead to an increase in intraabdominal adhesion formation; conversely, it decreased adhesion severity. Nevertheless, the agent led to increased acute and chronic inflammatory changes in the lungs and serosal surfaces of the intestines with minor architectural changes in the liver. Further studies with various application doses and routes with more detailed cellular analysis are thus warranted to clarify the possible pleiotropic and adverse effects of this new agent away from hemostasis.

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