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ORIGINAL ARTICLE

Effects of sugammadex on the prevention of postoperative peritoneal adhesions

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Abstract Many materials and techniques have been used to prevent and repair intra-abdominal adhesions, but an effective solution has not been found. The aim of this study is to research the effect of sugammadex on intra-abdominal adhesions in an experimentally induced intra-abdominal adhesion model. Twenty-four female Wistar albino rats were included in the study. The experimental animals were randomly divided into three groups: the sugammadex group (Group SX, $n = 8$), the control group (Group C, $n = 8$), and the sham group (Group S, $n = 8$). After starvation for 1 night, the rats were injected with a 50 mg/kg intramuscular dose of ketamine and a 5 mg/kg intramuscular dose of xylazine for anesthesia. The rats in the SX group were given 3 mL sugammadex into the peritoneal cavity, while rats in the control group were given 3 mL 0.9% sodium chloride. In the sham group, the peritoneal cavity was opened, but no chemicals were administered. All rats were sacrificed on the 10th postoperative day. The adhesions were staged as 0, 1, 2, and 3 according to Evans et al.'s model. Our evaluation of macroscopic adhesion intensity found statistically significant differences between the groups. The sugammadex group was observed to have fewer adhesions in a statistically significant manner compared with the control group ($p < 0.05$). In our experimental intra-abdominal adhesion model in rats, we observed that sugammadex prevented postoperative intra-abdominal adhesions.
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Introduction

Postoperative adhesions are frequently seen after abdominal surgery [1,2]. It is estimated that >90% of all surgical procedures may cause adhesions [3]. These adhesions are a major clinical problem after surgery [3,4]. Intra-abdominal adhesions may cause many complications such as intestinal obstruction, chronic abdominal pain, infertility, and extended hospital stays. Additionally, nearly a third of these patients require repeated operation under emergency conditions [5]. Studies have determined that the real cause of mortality and morbidity in 60–70% of patients with intra-abdominal adhesions is intestinal obstruction [6–8]. Many materials and techniques have been used to prevent and repair the problem, but an effective solution has not been found. Recent studies have focused on the formation of a mechanical barrier between peritoneal surfaces. To prevent postoperative peritoneal adhesions, the most frequently used methods involve administering a variety of fluids and drugs within the peritoneum. Many agents such as phospholipase inhibitors, dextrans, corticosteroids, phospholipids, and methylene blue have been tested according to literature [9,10]. For this mechanical barrier, gelatin-like fluids with high viscosity have been found to be more effective because these high-viscosity fluids form a layer preventing surfaces in the area of the peritoneum from contacting surrounding tissue and preventing adhesions [11,12]. Among prophylactic solutions used to prevent adhesions, the most frequently used agent is a high-molecular weight dextran solution, which covers surfaces and has a siliconizing effect that prevents contact between injured surfaces. A new agent, called sugammadex, is a water-soluble glucose polymer with a γ-cyclodextrin structure. Sugammadex selectively binds to nondepolarizing blockers with a steroid structure, like rocuronium, used as a muscle relaxant during general anesthesia. It safely and quickly reverses the deep neuromuscular blockage induced by rocuronium [13–16].

The aim of this study is to research the effect of sugammadex on intra-abdominal adhesions in an experimentally induced intra-abdominal adhesion model.

Methods

Required permissions for the study were obtained from Canakkale Onsekiz Mart University Experimental Animals Ethics Committee (2014/03-01; Çanakkale, Turkey). The study was completed in the Canakkale Onsekiz Mart University Experimental Animals Research Center in Turkey.

Experimental groups

Twenty-four female Wistar albino rats (mean weight: 300 $\pm$ 25 g; mean age: 5 months) were included in the study. The experimental animals were randomly divided into three groups: the sugammadex group (Group SX, $n = 8$), the control group (Group C, $n = 8$), and the sham group (Group S, $n = 8$).

Surgical technique

After starvation for 1 night, the rats were injected with a 50 mg/kg intramuscular (IM) dose of ketamine and a 5 mg/kg IM dose of xylazine for anesthesia. After the midline of the abdomen was shaved, antisepsis was provided with povidone iodine. With a 3 cm vertical midline incision, the peritoneal cavity was entered. The cecum and terminal ileum were found and placed on a damp gauze pad. With a dry gauze pad, the cecum and 2 cm of the terminal ileum were scraped. This procedure continued until the petechial hemorrhage foci were observed (scraping model) [17]. Later, rats in the SX group ($n = 8$) were given 3 mL (300 mg) sugammadex (Bridion, Schering-Plough Corporation, Oss, The Netherlands) into the peritoneal cavity, while rats in the control group (Group C, $n = 8$) were given 3 mL 0.9% sodium chloride. Rats in the sham group (Group S, $n = 8$) only had a 3 cm vertical incision completed and the peritoneal cavity entered, but no chemicals were administered to these animals. The incision was closed with the continuous stitch technique using propylene thread. After the 24 hour postoperative check, the rats were allowed to feed. All rats were given a 50 mg/kg IM dose of ketamine and a 5 mg/kg IM dose of xylazine for sufficient anesthesia on the 10th postoperative day and were sacrificed. To see the adhesions and to determine the correct staging, the peritoneal cavity was entered through an "inverse U" incision. Without disturbing the flap adhesions on the abdominal anterior wall, the abdominal anterior wall was pulled to caudal. Evans et al.'s [18] scoring was performed by general surgeons who were blinded to group allocation. The adhesions were staged as 0, 1, 2, and 3 according to Evans' model (Table 1).

Statistical analysis

All statistical analysis was performed using SPSS 15 (SPSS Inc., Chicago, IL, USA) statistical software for Windows. A nonparametric test, called the Chi-square test, was used to compare data from the sugammadex and control groups. A p value < 0.05 was considered significant.

Results

Our evaluation of macroscopic adhesion intensity showed statistically significant differences between the groups. When compared in terms of adhesion score 0, a limited significant difference was observed between the sugammadex group and the control group ($p = 0.05$). When compared in terms of adhesion score 1, a significant difference was observed between the sugammadex group and the control group ($p = 0.02$). When compared in terms of adhesion score 2, a significant difference was observed between the sugammadex group and the control group ($p = 0.03$). Finally, when compared in terms of adhesion score 3, a limited significant difference was also observed between the sugammadex group and the control group ($p = 0.05$).

In Table 2 the evaluation of macroscopic adhesions according to Evans et al.'s [18] model indicates that the

Table 1 Evans adhesion scoring.

Score	Description
0	No adhesions
1	Spontaneously separating adhesion
2	Separation of adhesion with traction
3	Separation of adhesion with a sharp dissection

sugammadex group had three score 0 adhesions (Figure 1), four score 1 adhesions (Figure 2), and one score 2 adhesion (Figure 3), whereas the control group had five score 2 adhesions (Figure 3) and three score 3 (Figure 4) adhesions. In the experimental animals of the sham group, only one was observed to have a score 1 (Figure 2) adhesion. We observed an adhesion to the abdominal wall of a single rat in the control group (Figure 4).

Discussion

In this study of an experimental intra-abdominal adhesion model in rats, we observed that sugammadex prevented intra-abdominal adhesions.

Injury of peritoneal surfaces by factors such as mechanical, lavage, thermal, infection, and foreign bodies begin events that result in the formation of adhesions. Injury of peritoneal mesothelial cells causes a release of thromboplastin, activating the clotting mechanism, which results in the formation of fibrin. Extreme fibrin production or weakened peritoneal plasminogen activator activation means the fibrin is not removed from the environment and forms a matrix for the development of adhesions [19—21]. In the damaged peritoneal region, there is an exudate rich in fibrin that forms a band between surfaces in contact. The fibrin bands and the spaces between these fibrin bands form a matrix rich in hyaluronic acid, creating an appropriate environment for collagen synthesis, which results in an adhesion [19—21]. Agents used to prevent adhesions are effective on mechanisms at any stage of the activated peritoneal damage and resulting adhesion formation [19—21]. Many different materials and methods have been used to prevent postoperative adhesions, but their clinical use is limited because most have been unsuccessful [22—24]. Preventing the accumulation of fibrin from

Table 2 The number of rats with different grades of adhesions in the three groups.

Adhesion scores	Group SX $n = 8$	Group C $n = 8$	Group S $n = 8$	p
Score 0	3	0	7	0.05
Score 1	4	0	1	0.02
Score 2	1	5	0	0.03
Score 3	0	3	0	0.05

Group C = control group; Group S = sham group; Group SX = sugammadex group.

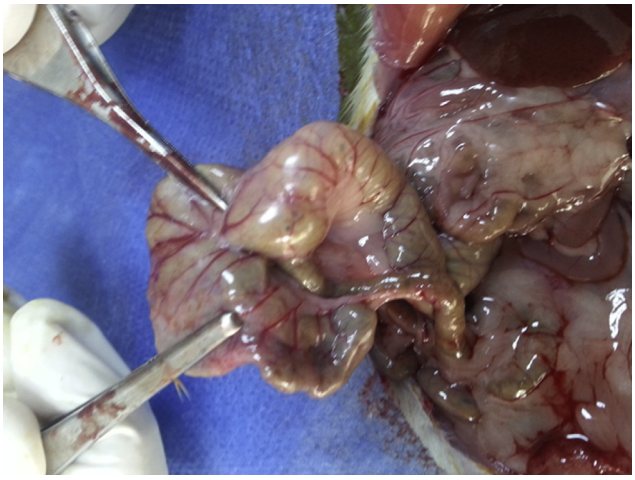

Figure 1. Grade 0 adhesion.

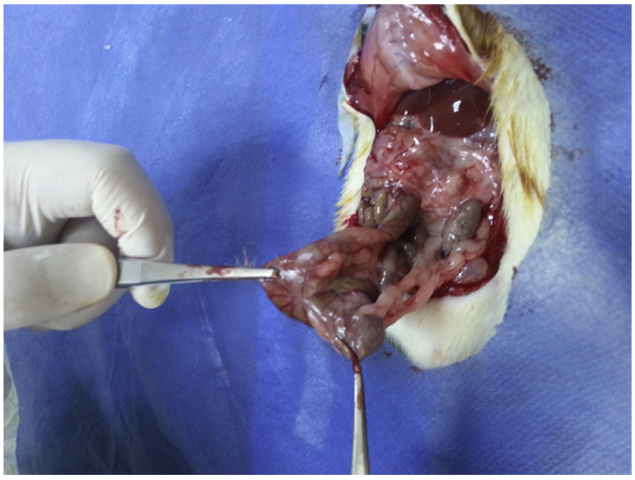

Figure 2. Grade 1 adhesion.



Figure 3. Grade 2 adhesion.

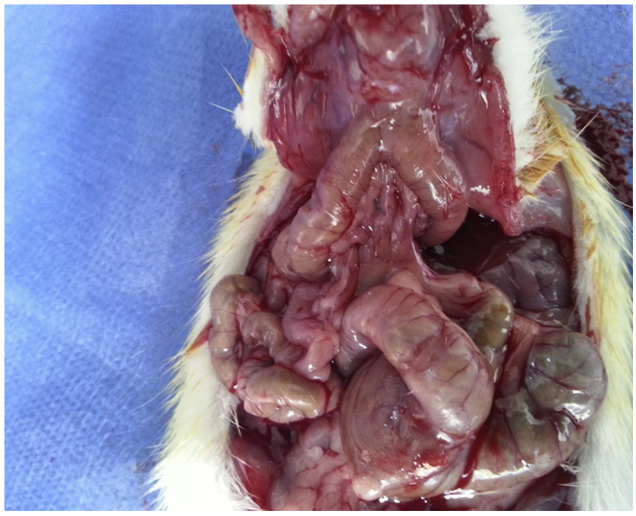

Figure 4. Grade 3 adhesion.

peritoneal exudate has been attempted with sodium citrate, heparin, and other anticoagulants. A variety of fibrinolitic agents, salts like sodium risonilate, and mechanical peritoneal lavage have been used to remove accumulated fibrin [25,26].

Dextran is a water-soluble glucose polymer used as a plasma expander. Among prophylactic solutions, the most commonly used to prevent adhesions is a high molecular weight dextran solution.

In an experimental study [27] when the effects of chitosane and a chitosane-dextran (CD) gel mixture on intra-abdominal adhesions were compared, CD gel prevented intra-abdominal adhesions better than chitosane. While CD gel prevented intra-abdominal adhesions, it was determined to inhibit fibroblast proliferation and physically separate the injured peritoneal surfaces.

Sugammadex is a compound from the cyclic oligosaccharide family. It is a medication that binds to steroid-structured nondepolarizing muscle relaxants and its use is continually increasing. Sugammadex reverses paralysis by coating free-circulating nondepolarizing muscle relaxants. It is superior to anticholinesterase because it reverses neuromuscular blockage rapidly and effectively, and reduces the recovery time [28]. Our review of the literature found no studies using sugammadex, which resembles dextran in structure, to prevent intra-abdominal adhesions. Sugammadex is viscous, allowing it to coat the damaged peritoneal surfaces with a siliconizing effect, and we believe this action will prevent the damaged surfaces from coming into contact with each other. However, similar to dextran [29], it may result in temporary acid formation, causing the intestines to float in this acid. We believe that with these effects sugammadex will prevent adhesions in the early period.

Different classifications are used to stage intra-abdominal adhesions. The stages described by Evans et al. [18] classify adhesions as 0, 1, 2 or 3 based on severity of adhesions of the serosal surfaces. The severity of adhesions plays a large role in the development of complications linked to postoperative peritoneal adhesions. As a result of this realistic aspect and its practical application, our study used Evans et al.'s [18] model to stage adhesions. When compared with the control group in our study, the sugammadex group was observed to have significantly fewer postoperative intra-abdominal adhesions. High viscosity sugammadex is not absorbed by the peritoneal lymphatics, so it stays in the peritoneal cavity for a long time, preventing damaged peritoneal surfaces from touching and, we believe, preventing adhesion of these surfaces.

Postoperative ileus cases due to the development of intra-abdominal adhesions is one possible complication, which is encountered more frequently after repeated surgery. As a result, we found that increasing the incidence of ileus condition further intensifies the development of the adhesion [25]. When compared in terms of adhesion score 2, a significant difference was observed between the sugammadex group and control group. When compared in terms of adhesion score 3, a limited significant difference was observed between the sugammadex group and control group. Therefore, we believe that sugammadex is important for reducing the degree of prevention of postoperative adhesions, as well as intra-abdominal adhesions.

In conclusion, we observed that sugammadex prevented postoperative intra-abdominal adhesions in our experimental intra-abdominal adhesion model in rats. However, a variety of clinical studies are required for sugammadex to be used to prevent postoperative peritoneal adhesion in humans.

References

[1] Ellis H. The clinical significance of adhesions: focus on intestinal obstruction. Eur J Surg 1997;577:S5—9.
[2] Menzies D. Peritoneal adhesions. Incidence, cause, and prevention. Surg Annu 1992;24:27—45.
[3] Menzies D. Postoperative adhesions: their treatment and relevance in clinical practice. Ann R Coll Surg Engl 1993;75:147—53.
[4] Menzies D, Ellis H. Intestinal obstruction from adhesions — How big is the problem? Ann R Coll Surg Engl 1990;72:60—3.
[5] Comert M, Karakaya K, Barut F, Karadeniz Cakmak G, Uçan HB, Gultekin FA. Does intraabdominal use of Ankaferd Blood Stopper cause increased intraperitoneal adhesions. Ulus Travma Acil Cerrahi Derg 2010;16:383—9.
[6] Cox MR, Gunn IF, Eastman MC, Hunt RF, Heinz AW. The operative etiology and types of adhesions causing small bowel obstruction. Aust N Z J Surg 1993;63:848—52.
[7] Parker MC, Ellis H, Moran BJ, Thompson JN, Wilson MS, Menzies D, et al. Postoperative adhesions: ten-year follow-up of 12,584 patients undergoing lower abdominal surgery. Dis Colon Rectum 2001;44:822—30.
[8] Ellis H. The magnitude of adhesion related problems. Ann Chir Gynaecol 1998;87:9—11.
[9] Aarons CB, Cohen PA, Gower A, Reed KL, Leeman SE, Stucchi AF, et al. Statins (HMG-CoA reductase inhibitors) decrease postoperative adhesions by increasing peritoneal fibrinolytic activity. Ann Surg 2007;245:176—84.
[10] Bae JS, Ahn SJ, Yim H, Jang KH, Jin HK. Prevention of intraperitoneal adhesions and abscesses by polysaccharides isolated from Phellinus spp in a rat peritonitis model. Ann Surg 2005;241:534—40.
[11] Wallwiener M, Brucker S, Hierlemann H, Brochhausen C, Solomayer E, Wallwiener C. Innovative barriers for peritoneal adhesion prevention: liquid or solid? A rat uterine horn model. Fertil Steril 2006;86:1266—76.

[12] Dizerega GS, Cortese S, Rodgers KE, Block KM, Falcone SJ, Juarez TG, et al. A modern biomaterial for adhesion prevention. J Biomed Mater Res B Appl Biomater 2007;81:239—50.
[13] De Boer HD, van Egmond J, van de Pol F, Bom A, Booij LHDJ. Chemical encapsulation of rocuronium by synthetic cyclodextrin derivatives: reversal of ne-uromuscular block in anaesthetized Rhesus monkeys. Br J Anaesth 2006;96:201—6.
[14] Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. Anesth Analg 2007;104:575—81.
[15] Brull SJ, Naguib M. Selective reversal of muscle relaxation in general anesthesia: focus on sugammadex. Drug Des Dev Ther 2009;3:119—29.
[16] Rex C, Bergner UA, Pühringer FK. Sugammadex: a selective relaxant-binding agent providing rapid reversal. Curr Opin Anaesthesiol 2010;23:461—5.
[17] Elkins TE, Bury RJ, Ritter JI. Adhesion prevention by solutions of sodium carboxymethylcellulose in rat. Fertil Steril 1984;41:926—8.
[18] Evans DM, McAree K, Guyton DP, Hawkins N, Stakleff K. Dose dependency and wound healing aspects of the use of tissue plasminogen activator in the prevention of intra-abdominal adhesions. Am J Surg 1993;165:229—32.
[19] Gül A, Kotan Ç, Şahin G, Timurkan H, Eryavuz Y. The effectiveness of intraperitoneal usage of hydroxyprogesterone caproate in prevention of postoperative adhesion: an experimental study. East J Med 1999;4:85—7.
[20] Karabulut E. Intra-abdominal adezyonlar. Fırat Üniversitesi Sağlık Bilimleri Dergisi 2001;15:417—22.
[21] Gül A, Kotan Ç, Dilek I, Gül T, Taş A, Berktaş M. Effects of methylene blue, indigo carmine solution and autologous erythrocyte suspension on formation of adhesions after injection into rats. J Reprod Fertil 2000;120:225—9.
[22] Alponat A, Lakshminarasappa SR, Teh M, Rajnakova A, Moochhala S, Goh PM, et al. Effects of physical barriers in prevention of adhesions: an incisional hernia model in rats. J Surg Res 1997;68:126—32.
[23] Nair SK, Bhat IK, Aurora AR. Role of proteolytic enzymes in the prevention of postoperative intraperitoneal adhesions. Arch Surg 1974;108:849—53.
[24] Canturk NZ, Vural B, Cubukcu A, Duzcen E, Utkan Z, Dulger M. Experimental study on the role of mast cells in peritoneal adhesion formation. East Afr Med J 1999;76:233—6.
[25] Ouaïssi M, Gaujoux S, Veyrie N, Denève E, Brigand C, Castel B, et al. Post-operative adhesions after digestive surgery: their incidence and prevention: review of the literature. J Visc Surg 2012;149:e104—14.
[26] DeCherney AH, diZerega GS. Clinical problem of intraperitoneal postsurgical adhesion formation following general surgery and the use of adhesion prevention barriers. Surg Clin North Am 1997;77:671—88.
[27] Lauder CI, Garcea G, Strickland A, Maddern GJ. Use of a modified chitosan-dextran gel to prevent peritoneal adhesions in a rat model. J Surg Res 2011;171:877—82.
[28] Fuchs-Buder T, Meistelman C, Raft J. Sugammadex: clinical development and practical use. Korean J Anesthesiol 2013;65:495—500.
[29] Wagaman R, Ingram JM, Rao PS, Saba HI. Intravenous versus intraperitoneal administration of dextran in the rabbit: effects on fibrinolysis. Am J Obstet Gynecol 1986;155:464—70.