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RESEARCH ARTICLE

An Assessment of the Application of Poloxamer/Sodium Alginate/$CaCl_2$ Mixture after Abdominal Surgery in Dogs: Effects on Postoperative Adhesion and Safety

Jina Kim, Sohee Bae, Li Li, Junemoe Jeong, Aeri Lee, Hyunjoo Lim, Oh-kyeong Kweon and Wan Hee Kim*

Department of Veterinary Clinical Science, College of Veterinary Medicine, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 151-742, Korea
*Corresponding author: whkim@snu.ac.kr

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ABSTRACT

Poloxamer/sodium alginate/$CaCl_2$ (PX/SA) mixture (Aniguard®, Genewel, South Korea) is a temperature-sensitive anti-adhesive agent used to prevent postoperative adhesion by forming a biocompatible barrier on the surface of a wound. This study investigated the safety and the ability of PX/SA mixture to prevent postoperative adhesion in dogs. Twenty dogs were divided into two experimental models: an intestine model and a uterus-urinary bladder model. Each model was further divided into two groups. Dogs in the intestine model underwent laparotomy, with multiple intestinal wall abrasions, while dogs in the uterus-urinary bladder model underwent urinary bladder wall abrasion. The control groups were treated with normal saline, and the trial groups were treated with PX/SA mixture. After 10 days, all dogs underwent a laparoscopic exploration to evaluate their abdominal status. On postoperative day 21, the abdominal adhesions were evaluated and scored by a previously validated adhesion score system. Furthermore, the extent of fibrosis and inflammation was scored according to a histopathologic examination. The adhesion scores of the trial groups were significantly reduced in both models compared to those of the control groups. Furthermore, more fibrosis reactions were found on the adhesion areas in the control groups in both models. There were no statistically significant differences in inflammation between the two groups. In addition, no hepatic and renal toxicity or side effects of PX/SA mixture were observed. In conclusion, the use of PX/SA mixture effectively reduced the development of postoperative abdominal adhesions.

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INTRODUCTION

Adhesion is an abnormal pathological bond between tissues or organs that need to be kept separated (Vrijland *et al.*, 2003). As part of the normal healing process after an injury, it is resolved within 5–6 days by absorption of inflammatory and fibrous cells (diZerega, 2001). However, various factors, such as bleeding, infection, ischemic changes, and intraperitoneal foreign bodies (Ozel *et al.*, 2005), can cause a fibrin matrix to remain at the site of injury, thereby causing abnormal adhesion.

Intra-abdominal adhesions frequently form in patients after laparotomy or laparoscopic surgery (Levrant *et al.*, 1997). Although adhesion can have positive effects, it can sometimes lead to major clinical problems, causing significant effects on morbidity and mortality (Ellis *et al.*, 1999). For example, it can cause intestinal inflammation, intestinal obstruction, intestinal torsion, peritonitis, chronic pain, and malfunction. It can also increase the duration of surgery and the number of complications due to the need for subsequent reoperations. Problems associated with adhesion are a major issue not only in human medicine but also in veterinary medicine. For this reason, there have been many different attempts to prevent adhesion, with much research focusing on anti-adhesion agents (Attard and MacLean, 2007).

An effective anti-adhesion agent should prevent adhesion without delaying wound healing. It should also be quick and easy to apply, and must be biocompatible. Current film-type anti-adhesion agents have advantages, such as good fixation strength and the ability to be applied to a broad area. However, the areas in which they can be

applied are limited, and the film needs to be cut to cover the specific area (Becker *et al.*, 1996). Unlike film-type agents, solution-type agents are easy to use and can be applied quickly. However, their fixation performance is poor (Park *et al.*, 2011).

Poloxamer/sodium alginate/$CaCl_2$ (PX/SA) mixture (Aniguard®, Genewel, South Korea) is effective in preventing postoperative adhesion and forms a biocompatible barrier on the surface of a wound. In human medicine, PX/SA mixture has been proven to be safe and effective in a number of clinical experiments in many different fields, and it is commonly used in human medicine practice (Hong *et al.*, 2011; Park *et al.*, 2013; Sohn *et al.*, 2013).

The purpose of this study was to demonstrate the utility of PX/SA mixture in the prevention of intra-abdominal adhesion formation after abdominal surgery in dogs, focusing on the product's effectiveness and safety.

MATERIALS AND METHODS

This study was approved by institutional animal care and use committees of Seoul National University.

Experimental groups: Twenty female beagle dogs were included in this study. Dogs that had previously undergone abdominal surgery were excluded and divided into two experimental groups, with each group subdivided into two groups of equal number.

Induction of adhesions: The same surgical team performed all of the procedures in sterile conditions. In Experiment 1 (The intestine model) the entire abdominal cavity was explored, and dogs with existing abdominal adhesions were excluded. The ileocecal junction was identified, and homogenous petechial hemorrhages were created on the intestinal serosa (1.0 × 1.0 cm) by scraping with a No. 15 blade at a distance of 3 cm from the cecum. Five distinct surgical lesions were made at intervals of 3 cm. The adjacent intestinal loop was then sutured with 4-0 polydioxanone (PDS® II, Ethicon, United Kingdom) at three equally distant points to induce adhesion.

In Experiment 2 (The uterus-urinary bladder model), all of the procedures were the same as those used in the intestine model. Homogenous petechial hemorrhages were created on the urinary bladder serosa (1.0×1.0 cm) by scraping with a No. 15 blade. One surgical lesion was made. The adjacent uterus body was then sutured with 4-0 PDS® II at one point.

After adequate hemostasis was achieved, abdominal lavage was performed using normal saline. In the control group, each lesion was coated with normal saline. In the trial group, the abraded tissues and adjacent organ were coated with PX/SA mixture.

Midterm exploratory laparoscopy: Each dog was placed in a dorsal recumbent position, and exploratory laparoscopy was performed using a two-cannula technique. A veress needle was inserted and a pneumoperitoneum was then established with CO_2 (maximal pressure, 10–15 mmHg). The site for the initial trocar was a few centimeters craniolateral to the umbilicus on the right side. A laparoscope was inserted into the abdomen to explore the abdominal cavity. A second trocar was also inserted on the contralateral side for additional exploration.

Macroscopic evaluation: Ten days after the surgery, laparoscopy was performed to assess the extent of adhesions and possible complications. Twenty-one days after the surgery, relaparotomy was conducted to perform a macroscopic evaluation of the adhesion. The grade and severity of the adhesions were blindly evaluated by two surgeons. A previously validated adhesion score system (Belluco *et al.*, 2001) was used to evaluate the intra-abdominal adhesions (Table 1).

Microscopic evaluation: The adhesive sites including adjacent normal tissue were excised to evaluate histologic findings on postoperative day 21. A histopathologic examination was performed under a light microscope (BX50F4, Olympus Optical CO, Japan). The degree of fibrosis and inflammation was evaluated with the previously validated score system (Hooker *et al.*, 1999) (Table 2).

Table 1: Adhesion score system for macroscopic evaluation.

Adhesion characteristics	Score
Extent of site involvement	
None	0
<25%	1
<50%	2
<75%	3
<100%	4
Type	
None	0
Filmy, transparent, avascular	1
Opaque, transparent, avascular	2
Opaque, capillaries present	3
Opaque, large vessels present	4
Tenacity	
None	0
Adhesion falls apart	1
Adhesion lysed with traction	2
Adhesion requiring sharp dissection	3
Possible total	11

Table 2: Adhesion score system for microscopic evaluation.

Fibrosis grade	Inflammation grade	Score
None	None	0
Minimal, loose	Giant cells, lymphocytes, plasma cells	1
Moderate	Giant cells, eosinophils, neutrophils	2
Florid dense	Many inflammatory cells, microabscess	3

Evaluation of safety: To evaluate the hepatic and renal toxicity of PX/SA mixture, a blood test was performed on the preoperative day and on postoperative days 1, 7, 14, and 21. The liver and kidney were harvested on postoperative day 21. All of the samples underwent histopathologic examination.

Statistical analysis: The results were analyzed with regard to statistical significance using nonparametric Mann-Whitney U-test. A *P* value of less than 0.05 was considered statistically significant. Data are reported as mean values, with the variability expressed as standard deviation.

RESULTS

Assessment of adhesions and complications: During the entire experiment, the animals were observed for general conditions, such as vitality, appetite, vomiting, nausea, fever, abdominal pain, dehydration, rash, and inflammation. The results revealed nothing of significance. Evaluations after both the midterm laparoscopy and relaparotomy showed no complications, such as peritonitis, inflammatory responses, or delayed wound healing. During the experimental period, none of the groups experienced incisional hernias, intra-abdominal abscesses, or main wound dehiscence.

Macroscopic evaluation: Although it is difficult to make a full objective evaluation from a laparoscopy, on a subjective level, the number of adhesions was reduced in the group that received PX/SA mixture. The abdominal cavity of the control group could not be fully evaluated because of the attachment of the intestines to the peritoneum and the intertwining of intestines. The appearances of the adhesions for the control groups of both models are shown in Fig. 1. In both experiments, adhesion score was significantly ($P<0.05$) higher in the control groups as compared to trial groups (Table 3; Fig. 2).

Table 3: Macroscopic adhesion scores in all the groups of experiment

	Extent of site involvement	Type	Tenacity	Total score
Experiment 1: The intestine model				
Control group	3±0.70	2.6±0.54	2±0	7.6±0.89
Trial group	0.8±0.83	0.6±0.54	1.2±1.09	2.6±2.40
P value	0.008*	0.008*	0.31	0.008*
Experiment 2: The uterus-urinary bladder model				
Control group	1.6±0.89	1.6±0.5	2±0	5.2±0.83
Trial group	0.4±0.54	0.8±1.3	0.8±1.09	1.8±2.48
P value	0.056	0.222	0.151	0.032*

Data are reported as mean values, with the variability expressed as standard deviation; * Statistically significant from control groups in each experiment models ($P<0.05$).

Microscopic evaluation: Experiment 1: The intestine model: In the control group, the fibrosis score was 2.4±0.54. In trial group, it was 0.8±0.83. Statistical analysis indicated that the fibrosis score of the trial group was significantly lower than that of the control group ($P<0.05$). In the control group, the inflammation score was 0.4±0.89. In trial group, it was 0.2±0.44. Statistical analysis indicated that there is no statistical difference between the two groups.

Experiment 2: The uterus-urinary bladder model: In the control group, the fibrosis score was 2.2±0.44. In the trial group, it was 0.8±1.09. Statistical analysis indicated that the fibrosis score of the trial group was significantly lower than that of the control group ($P<0.05$).

In the control group, the inflammation score was 0±0. In the trial group, it was 0±0. Statistical analysis indicated that there is no statistical difference between the two groups. Histopathologic examinations of fibrosis and inflammation for all groups are shown in Fig. 3.

Adhesion frequency: In the intestine model, there were twenty-four adhesion sites in the control group and seven in the trial group. Although adhesion was also confirmed at various sites, the most frequent adhesion site in both groups was between the intestinal serosa. In the uterus-urinary bladder model, there were eight adhesion sites in the control group and two in the trial group. The most frequent adhesion site in both groups was the urinary bladder to broad ligament of the uterus. The second most frequent adhesion site in both groups was the urinary bladder to the uterine horn.

Safety evaluation:

Blood tests: The blood cell count test and blood chemistry test of the inflammatory response and major organ toxicity revealed no significant differences between the control and trial groups. The results of the blood analysis are shown in Fig. 4.

Histology of the liver and kidney: Abnormal histopathological changes were not detected in any of the animals. The appearance of the liver and kidney samples of both groups is shown in Fig. 5.

DISCUSSION

The incidence rate of adhesive intestinal obstruction after abdominal surgery has been increasing steadily over the years and surgical intervention is needed in most cases (Menzies and Ellis, 1990). Postoperative adhesion is also a frequent problem in the veterinary field. Therefore, active use of anti-adhesion agents, such as Poloxamer/sodium alginate/$CaCl_2$ (PX/SA) mixture, is urgently required in veterinary medicine. However, there have been a few studies 123 of its use in dogs and cats. Thus, there is a lack of information on appropriate dosages and its applicability in various types of surgery. Given the lack of clinical application of PX/SA mixture in the field, further studies are needed. Therefore, we investigated the utility of PX/SA mixture in the prevention of postoperative adhesion in dogs, focusing on the effects and safety of the product.

The results of the macroscopic and microscopic evaluation of adhesion in both models showed that the adhesion incidence was significantly reduced when PX/SA mixture was applied ($P<0.05$).

According to the macroscopic evaluation of adhesion, the most frequently observed adhesion site was between intestinal serosa in the intestine model (Singer *et al*., 1996). The adhesion formation rate increased in the order of intestinal serosa to parietal peritoneum, intestinal serosa to intestinal mesentery, intestinal serosa to falciform fat, and intestinal serosa to omentum. More adhesions were found in other areas, including the intestinal mesentery to parietal peritoneum. Keeping in mind that one of the main reasons for adhesion-induced intestinal obstruction is the adhesion between intestines, the results reveal the importance of preventing adhesion when performing abdominal surgery (diZerega, 2001; Attard and MacLean, 2007).

According to the microscopic evaluation, some inflammatory cells were found in localized areas in both groups of the intestine model. These included lymphocytes, plasma cells, macrophages, and neutrophils. However, the amount was very low, suggesting that the cells were not a pathological inflammatory reaction. Therefore, the application of PX/SA mixture does not cause inflammation (Hong *et al.*, 2011).

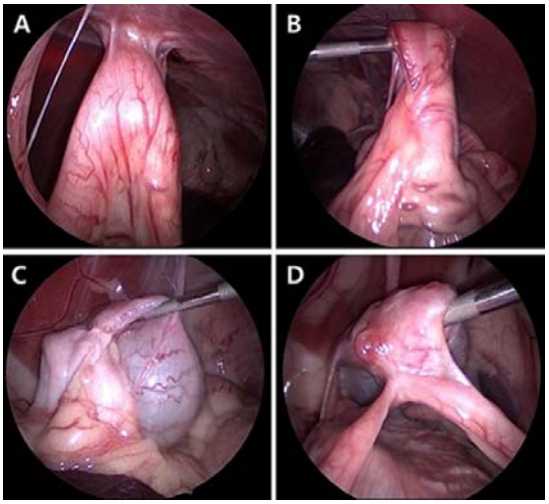

Fig. 1: Mid-term exploratory laparoscopy in the control groups of both models. (A), (B): Attachment of the intestines to the peritoneum and intertwining of the intestines were observed. (C), (D): The urinary bladder attached to the uterine horn and broad ligament of the uterus.

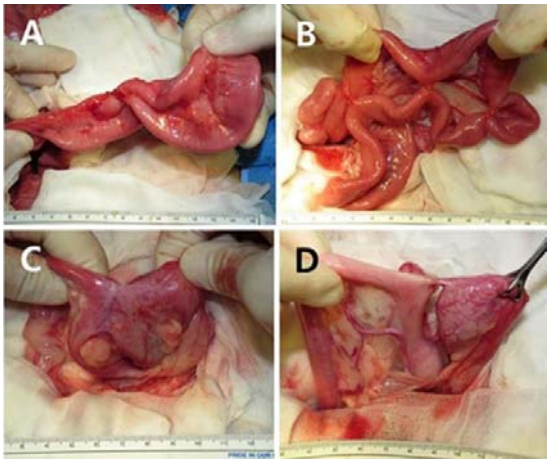

Fig. 2: Macroscopic adhesion. (A): In the control group of the intestine model, the most frequent adhesion site was between the intestinal serosa. (C): In the control group of the uterus-urinary bladder model, adhesion was confirmed between the urinary bladder, broad ligament of the uterus, and uterine horn. (B), (D): In the trial groups of both models, no adhesion was confirmed except at sutured sites.

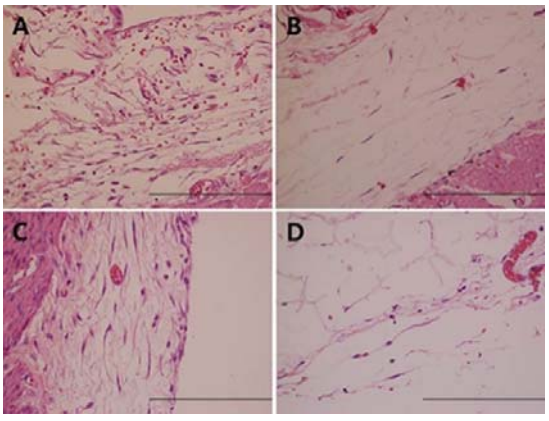

Fig. 3: Microscopic adhesion. Histopathological examinations of fibrosis and inflammation in all groups. (A), (C): In the control groups of both models, moderate to dense fibrosis was confirmed at adhesion sites. (B), (D): Relative to the control groups, loose fibrosis was confirmed in the trial groups of both models. (H & E stain, scale bars=200 μm).

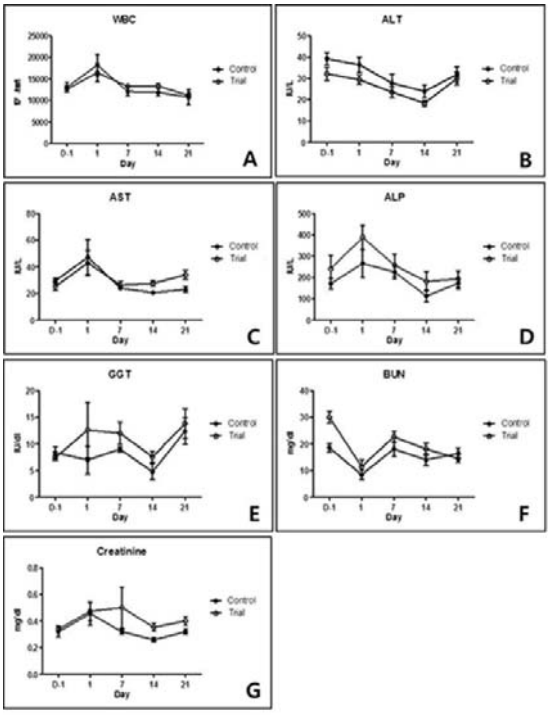

Fig. 4: Blood analysis. There is no statistical difference between the two groups (P<0.05). (A): WBC (B): ALT (C): AST (D): ALP (E): GGT (F): BUN (G): Creatinine.

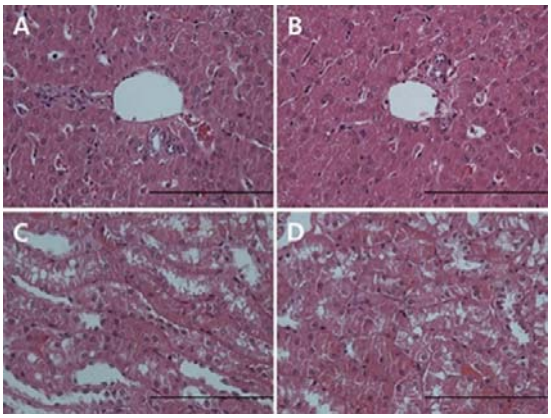

Fig. 5: Histology of the liver and the kidney. Abnormal histopathological changes were not detected in any of the animals. (A), (C): In the control groups (B), (D): In the trial groups. (H & E stain, scale bars=200 μm).

The blood test, which was conducted to evaluate the safety of PX/SA mixture, revealed no significant differences in the level of WBC, ALT, AST, ALP, GGT, BUN, and creatinine between the two groups. Although temporary increases in the values of WBC, AST, ALP, GGT, and Creatinine were identified after surgery, the values were identified to be within the normal range and later returned to preoperative values. Furthermore, histopathologic examination of the liver and kidney revealed no toxic change. Thus, the application of PX/SA mixture is harmless to the body and does not affect vital organs (Singh-Joy and McLain, 2007; Jeong *et al*., 2009).

PX/SA mixture is commercialized under the name of Guardix-SG® (Genewel, South Korea) in human medicine.

Guardix-SG® has already been shown to be effective and safe in preclinical and clinical experiments (Hong *et al.*, 2011; Park *et al.*, 2013; Sohn *et al.*, 2013). Aniguard®, which is made of same component as Guardix-SG®, is commercialized for use in veterinary clinical medicine. It is a safe, temperature sensitive anti-adhesion agent (Li *et al.*, 1996) that is made by poloxamer cross-linked sodium alginate and $CaCl_2$ to the biocompatible polymer. Poloxamer is widely used in the pharmaceutical field (Patel *et al.*, 2009) because it relatively well dissolves hydrophobic drugs and the component polyethylene glycol is hydrophilic (Singh-Joy and McLain, 2007) and known to prevent tissue adhesion by preventing cell attachment (Leach and Henry, 1990). However, the adhesion prevention efficacy is not easily maintain because polyethylene glycol is easily diluted and absorbed by body fluid. Therefore, cross-linked sodium alginate was added to increase the safety of poloxamer. Sodium alginate is easily cross-linked by divalent cations such as $CaCl_2$ to form a gel. So, PX/SA mixture has flowability under 25°C in the form of a solution and form a gel at room temperature greater than 25°C (Kwon *et al.*, 2006; Yu *et al.*, 2014). Therefore, not only can it be easily injected using syringes, but it also prevents adhesion by acting as a physiological barrier. It can be applied to many types of surgeries frequently performed in veterinary clinical medicine, such as gastrointestinal surgery, urolith removal, and other intra-abdominal surgeries where postoperative adhesion of the surrounding tissues can cause major clinical problems (Adin, 2011). Intra-abdominal surgery, especially gastrointestinal and urinary surgery, may be repeated because of the high recurrence risk of intestinal foreign bodies and urinary tract stones. Adhesions that occur after disk surgery make it difficult to expose a surgical window during reoperation. Furthermore, excessive traction while separating the adhesion and opening the surgical window may cause nerve damage (Songer *et al.*, 1990). In these situations, the application of PX/SA mixture reduces the risk of tissue damage and bleeding during separation of the adhesion, increases safety by shortening the reoperation time, and saves reoperation costs by preventing possible additional surgery and adhesion-induced complications (Ray *et al.*, 1998). It is anticipated that PX/SA mixture can be applied not only in abdominal and thoracic surgery, but also in orthopedic surgery (Yu *et al.*, 2012) where adhesion frequently occurs between tendons and ligaments (Oh *et al.*, 2011). Moreover, it can be used in other procedures, such as endoscopy, laparoscopy, and thoracoscopy. As a result, PX/SA mixture significantly reduced the development of postoperative abdominal adhesions, and had no hepatic and renal toxicity or side effects.

Conclusions: PX/SA mixture is an easy to use temperature-sensitive anti-adhesive agent, with "reverse thermal gelation" activity. Its application after various types of veterinary surgery is a very effective method for reducing adhesion formation. Moreover, it is harmless to vital organs and does not cause inflammation. We suggest that PX/SA mixture is an effective, convenient, and safe agent to prevent postoperative abdominal adhesion.

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