J Vet Clin 26(4) : 324-330 (2009)

Journal of Veterinary Clinics
www.ksvc.or.kr

The Effects of Poloxamer/Sodium Alginate Mixture Barriers on Prevention of Post-Operative Peritoneal Adhesion in Dogs

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(Accepted : August 18, 2009)

Abstract : This study was performed to determine the effectiveness of poloxamer/sodium alginate mixture(PX/SA) barriers on prevention of post-operative peritoneal adhesion in dogs. Fifteen mongrel dogs were divided into three experimental groups: non-treated group, 2% Sodium Carboxymethylcellulose (SCMC) treated group and PX/SA treated group. In order to induce adhesions, the anti-mesenteric serosa of the ileum was exteriorized and then abraded in a standard manner by scraping with a scalpel blade to create homogeneous petechial hemorrhagic surface over a 1 × 1 cm area. Solution of SCMC was allowed to spread across the intraperitoneal organs through a catheter using a syringe. PX/SA was simply coated over the abraded tissues. On day before and day 1, 4, 7, and 14 after operation, venous blood specimens were collected for measurement of RBC, total WBC and fibrinogen. The adhesions were blindly assessed 3 weeks later by using a computerized tensiometer. The RBC, total WBC and fibrinogen values of three groups showed no statistical significances. The mean tensile strength(gram force, gf) of formed adhesions on day 21 after surgery was 173.05 ± 113.48 in the non-treated group, 111.42 ± 38.25 in the SCMC group, and 69.00 ± 45.07 in the PX/SA group. The tensile strength values for adhesion seperation in PX/SA group was lower than those in SCMC group($p < 0.05$) and significantly lower than those in the non-treated group($p < 0.05$). Our data suggested that PX/SA should be effective on reducing peritoneal adhesion formation in dogs compared with SCMC. PX/SA may be applicable to preventing post-operative intraperitoneal adhesion in dogs.

Key words **:** poloxamer/sodium alginate mixture, peritoneal adhesions, tensile strength, dogs.

Introduction

Abdominal adhesions are defined as pathologic bonds between surfaces of the peritoneal or pelvic cavities formed during the scarring of peritoneal surface defects (4), that is, fibrinous or fibrous bands that form abnormal unions between two or more surfaces that are normally covered with the serosa (19). Postoperative intraperitoneal adhesion formation is a cause of anxiety, an important and so far unsolved surgical problem (29,32).

Postoperatively, adhesions may result from contamination with foreign materials such as gauze, glove powder, talc (magnesium silicate) crystals, antibiotic powders and immoderate drying of serosal surfaces, infection, traumatic handling of serosal tissue.

Adhesions happened in more than 94% of patients who were underwent major abdominal operations (3,5). Abdominal adhesions are common cause of mechanical bowel obstructions (1,9,21), female infertility (6,13), and then they may be related to chronic abdominal pain (18,24). In addition, intraperitoneal adhesions make subsequent abdominal operation more difficult and potentially hazardous.

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For this reason, to prevent or reduce the complication of intraperitoneal adhesions numerous studies have been done on animals (7). Various adjuvants have been tried to prevent postoperative adhesions, these are as follow: anti-inflammatory agents (NSAIDs, corticosteroids), antibiotics, rubricate (fluid) agents (normal saline, chlorohexidine, sodium carboxymethylcellose (31), hyaluronic acid, dextran 70), and antioxidative agents (vitamin E). In the past decade, significant progress has been made with the development of adhesion barriers. These include Gore-Tex® membrane; oxidized, regenerated cellulose (Interceed®) (2,14); and hyaluronic acid-carboxymethycellulose (HA-CMC) membrane (Seprafilm®; Genzyme, Somerville, NJ), (GUARDIX-MB®; BIORANE. Co., Ltd). Recently, thermo-sensitive gel as physical barrier that prevent adhesion formation by seperating defective tissue surface during the repair stage has become available for the abdominal surgery.

Sodium carboxymethylcellulose(SCMC) is clear and semigelatinous material. It is a substituted polysaccharide that is prepared by reacting sodium monochloracetate with cellulose. The material is heat-stable and sterilized by immersion in boiling water for 5minutes. The material is an ingredient in some protective ointments and is used as a thickener in many foods. Available food grade forms have a molecular weight as great as 350,000. The heavy molecular weight and

the viscosity of this solution are effective in separating serosal and peritoneal surfaces during the time of epithelial regeneration and thereby help prevent postoperative adhesions.

Poloxamer/sodium alginate mixture (PX/SA) is a thermosensitive gel that has lower critical solution temperature (LCST; reverse sol-gel transition temperature). This material is thermo-sensitive gel which means solution form in room temperature and transformed into gel form immediately after surgical operation because it is mixed poloxamer which is a kind of bioavailable polymer and alginate in certain rate. PX/SA is applied directly to specific sites of surgical trauma to provide a physical barrier that separates traumatized tissue from other tissues during normal healing. Composed of poloxamer and sodium alginate, PX/SA is slowly resorbed into the body, maintaining a barrier effect while the body's normal tissue repair takes place.

Accordingly this study demonstrated to evaluate the effectiveness of PX/SA barriers by comparing with SCMC capacity of which to prevent the formation of postoperative adhesions in a noninfectious environment is well known.

Materials and Methods

Experimental animals

Fifteen healthy adult mongrel dogs (weighing 3.99 ± 1.53 kg) were used in the study. All dogs were vaccinated with DHPPL and dewormed with febantel (Drontal® Plus, Bayer Korea Ltd., Korea). Experiments started after an initial adaption period for two weeks. The dogs resided in each cage, and the food and water were fed *ad libitum.* They were divided into three groups containing five dogs, respectively: non -treated group (NC), SCMC treated group, PX/SA treated group.

Preparation of materials

SCMC was used in a 2% SCMC solution which was prepared by boiling 200 ml of sterile water and adding 20 g of SCMC powder (Sigma Chemical Co., USA) while stirring. After the SCMC was in solution, additional sterile water was added while stirring to bring the total volume to 1 L, and then sterilized by autoclave before usage.

PX/SA was prepared by 30% polyethylene glycol-polypropylene glycol-polyethylene glycol (Poloxamer, BASF, Ludwigshafen, Germany), 0.6% sodium alginate (Sigma, St. Louis, USA), and 0.06% $CaCl_2$. This mixture was kindly provided by BIORANE. Co., Ltd.

Surgical Procedures

Food was withheld for 12 hours before surgery in all dogs. Anesthesia for surgery was similar for all groups. All dogs were administered atropine sulfate (Atropine®, Dai Han Pharm. Co., Korea, 0.05 mg/kg) subcutaneously. Ten minutes after atropine sulfate injection, the dog was administered tiletmine/zolazepam (Zoletil®, Virbac Co., Korea, 5 mg/kg) intramuscularly to induce and maintain the anesthesia. Dogs were positioned in dorsal recumbency and the entire abdomen was clipped. The surgical site was draped in a common manner. A 5 cm ventral midline incision was made through the skin, subcutaneous tissue, and peritoneum.

Control group : After the abdomen was opened, the ileum and ileocecal junction were examined and then exteriorized. Total five distinct surgical lesions were made in order to induce adhesions. The antimesenteric defects of the ileum approximately 5 cm from the ileocecal junction were created by light scraping about 1 × 1 cm areas with a sterile No. 10 scalpel blade to promote petechial bleeding, and allowed to air dry for 15 minutes. The nondefect areas of the small intestine were protected from drying by placing moist gauze over them during the drying period. In this group, none of adjuvant solutions were instilled into peritoneal cavity, and then the ileum was replaced in normal position. The abdominal wall was closed using a simple continuous pattern with 2-0 polyglactin 910 (Vicryl®, Johnson&Johnson Medical Korea Ltd., Korea) and the skin was closed by a simple interrupted pattern with 3-0 nylon (BLUE NYLON®, Ailee Co., Ltd).

SCMC Group : Antimesenteric defects to induce adhesions were created at five locations using a similar method described control group. In this group, 7 ml of 2% SCMC solution/kg was infused through the catheter, using a sterile syringe over a entire abdominal cavity, before closure. The catheter was then removed, and abdominal cavity was closed intactly. The abdominal cavity was closed using with same method used in control group.

PX/SA Group : Antimesenteric defects to induce adhesions were created at five locations using a similar method described control group. In this group, PX/SA gels were simply coated over the abraded tissues (0.5 ml/abraded area). And then the small bowel was returned to its original location. The abdominal cavity was closed using with same method used in control group.

One surgeon carried out all the operations and was blind to the randomization while he was performing the abrasions.

Postoperative Evaluations

The experimental animals were monitored daily for signs of postoperative pain, drainage, feed consumption or defecation. All dogs were administered enrofloxacin (Baytril, Bayer Korea Ltd., Korea, 5 mg/kg) subcutaneously to reduce the risk of postoperative infection for 3 days.

On preoperative day(day 1 before operation, –1), 1, 4, 7, and 14, venous blood specimens were collected from animals for hematological analysis; RBC, WBC, and fibrogen.

Assessments of Adhesion : Three weeks later, all the animals were again anesthetized and reopened through ventral midline incision, after cleaning with povidone-iodine solution and 70% alcohol. And then a postmortem examination was conducted immediately. Adhesions were identified, and the adhesion site was excised to test. The tensile strength of the adhesion site was evaluated with tensiometer (H500DM®, Hounsfield co., UK) (Fig 1). Both adhesive tissue ends were

(A) (B)

Fig 1. The tensiometer used in the measurement of the force required to separate adhesions. (A) The clamp of tensiometer. Both adhesive tissue ends were secured tightly in this clamp during the measurement of tensile strength. (B) The indicator of tensiometer. This shows breaking strength (gram forth, gf) of specimens and motion velocity (cm/min) of the clamp.

secured tightly in a clamp (Fig 1A) so as not to slip from the clamp during tensile test. The clamp was advanced at the rate of 0.7 cm/min. During the operation of tensiometer, breaking strength of specimens was measured (Fig 1B). Tests were performed at the room temperature of 20°C, and specimens were moistened with a very fine mist of normal saline while clamped.

Results

The second laparotomy was performed in all experimental groups at 3 weeks after surgery. All animals had insignificant postoperative signs during the experimental periods. The results of the hematological examination and adhesion assessments were tabulated below.

Laboratory Values

RBC

The ranges of RBC counts(M/mm^3) were from 5.19 ± 0.64 to 5.03 ± 0.82 in NC Group, from 5.55 ± 0.98 to 5.49 ± 0.74 in SCMC Group, and from 5.08 ± 0.57 to 5.50 ± 1.06 in PX/SA Group. The values among the control group and the treated groups showed no significant differences(Table 1).

Table 1. The changes of total RBC values after SCMC and PX/SA administration in dogs. (Mean ± SD, M/mm^3)

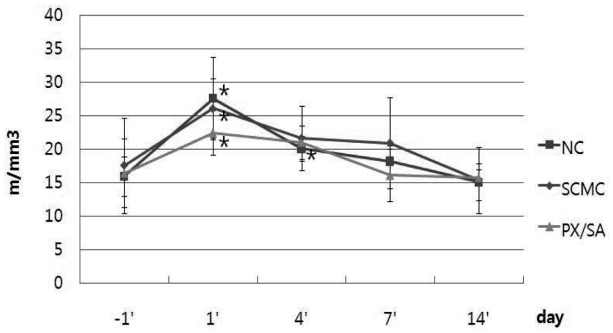
Day	NC	SCMC	PX/SA
-1	5.19 ± 0.64	5.55 ± 0.98	5.08 ± 0.57
1	5.65 ± 1.18	5.60 ± 0.84	5.25 ± 0.94
4	5.53 ± 0.62	5.60 ± 0.85	5.69 ± 0.55
7	5.53 ± 1.34	5.86 ± 0.66	5.62 ± 0.99
14	5.03 ± 0.82	5.49 ± 0.74	5.50 ± 1.06

WBC

The changes of WBC values (m/mm^3) were increased slightly from 15.94 ± 3.00 on day -1 to 27.57 ± 6.14 on day 1 NC Group, from 17.57 ± 7.10 to 26.07 ± 4.42 in SCMC Group, from 16.43 ± 5.07 to 22.41 ± 3.33 in PX/SA Group. The WBC values of control, SCMC, and PX/SA Group were 15.09 ± 2.81, 15.39 ± 4.93, and 15.74 ± 1.26 on day 14, respectively. The values among the control group and the treated groups showed no significant differences (Fig 2).

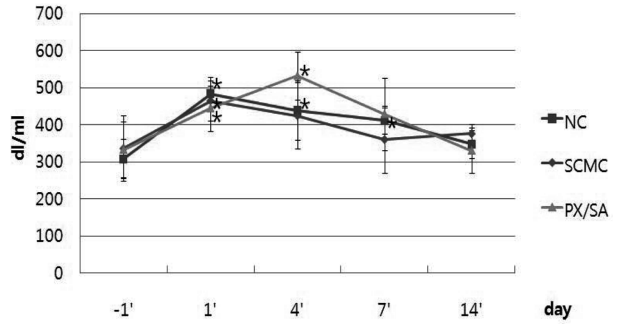
Fibrinogen

The fibrinogen concentration values (mg/dl) were increased slightly from 308.8 ± 53.03 on day −1 to 484.2 ± 44.19 on day 1 NC Group, from 336.2 ± 88.32 to 465.4 ± 53.65 in SCMC Group, from 334 ± 75.44 to 445.2 ± 61.09 in PX/SA Group. The values of PX/SA group were increased continuously from 445.2 ± 61.09 on day 1 to 532.2 ± 65.42 on day 4. The fibrinogen concentration values of NC, SCMC, and PX/SA Group were 348.2 ± 37.88, 376.2 ± 26.24 and 331.2 ± 60.71 on day 14, respectively. The values among the control group and the treated groups showed no significant differences (Fig 3).



*p < 0.05

Fig 2. The changes of total WBC counts after SCMC and PX/SA administration in dogs. (Mean ± SD, m/mm^3).



* $p < 0.05$

Fig 3. The changes of total fibrinogen concentrations after SCMC and PX/SA administration in dogs. (Mean ± SD, mg/dl).

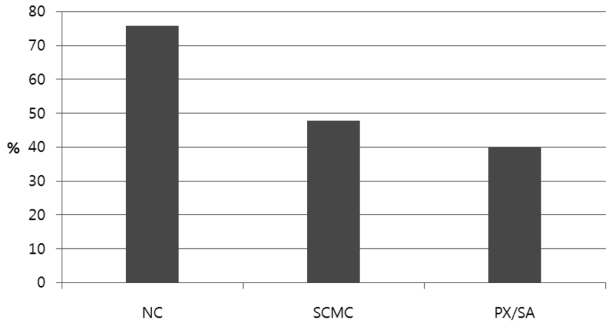


Fig 5. Adhesion incidences in each group on day 21 after operation.

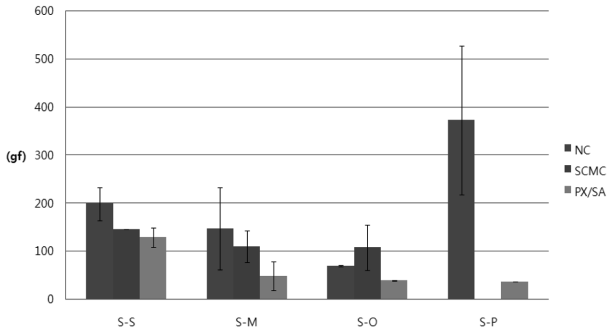


Fig 6. The mean strength values of each site in each group for adhesion separation.

Assessments of Adhesions

Three weeks after induction of peritoneal adhesions, the peritoneums were inspected for the locations (Table 2), incidences (Fig 5) and tensile strength (Fig 6, Fig7). All of the animals were admitted for occurrences of adhesions.

Gross appearance of intraperitoneal adhesion in NC group was dense and broad, but that in SCMC group and that in PX/SA group were filmy and thin (Fig4).

Adhesions were identified in total sites; serosa to mesentery (22 of 75, 29.33%), serosa to serosa (8 of 75, 10.67%), serosa to omentum (8 of 75, 10.67%), and serosa to parietal peritoneum (3 of 75, 4%) (Table 2).

Adhesion incidences were 76% in NC group, 48% in SCMC group, 40% in PX/SA group. Values of adhesion incidence in PX/SA group were reduced, compared with those in other groups (Fig 5).

The mean strength (gram force, gf) of the adhesion separation in each sites ; serosa to serosa (198.50 ± 34.30 gf), serosa to mesentery (146.36 ± 85.38 gf), serosa to omentum (69.50 ± 1.50 gf), serosa to parietal peritoneum (372.50 ± 155.50 gf) in NC group, serosa to serosa (145 gf), serosa to mesentery (109.14 ± 32.82 gf), serosa to omentum (107.00 ± 46.83 gf) in SCMC group, and serosa to serosa (128.67 ± 20.34 gf), serosa to mesentery (47.75 ± 30.14 gf), serosa to omentum (38.50 ± 0.50 gf), serosa to parietal peritoneum (36 gf) in PX/SA group (Fig 6).

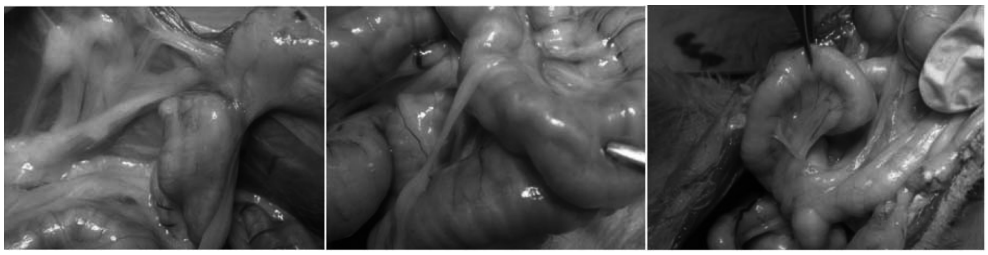
The mean adhesion separation strength (gram force, gf) was 173.05 ± 113.48 gf in NC group, 111.42 ± 38.25 gf in SCMC group, and 69.00 ± 45.07 gf in PX/SA group (Fig 7).

Values of adhesion separation strength in SCMC group were significantly reduced, compared with those in NC group ($P < 0.05$). Values of adhesion separation strength in PX/SA group were significantly reduced, compared with those in NC group ($P < 0.05$) and those in SCMC group ($P < 0.05$).

Discussion

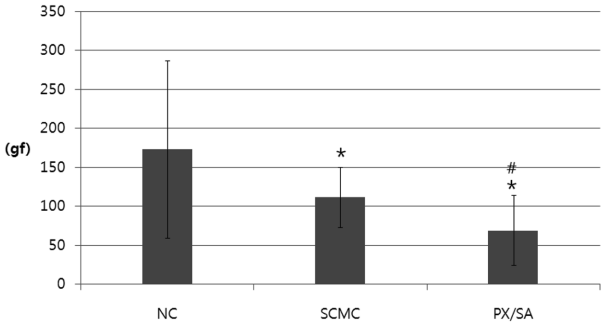
This study has demonstrated the efficacy of PX/SA on the prevention of postoperative adhesion formation in dogs. we have compared anti-adhesive effects when SCMC was used in the traumatized small bowel.

It is commonly believed that postoperative adhesion formation occurs when two injured tissue surfaces make contact



(A) (B) (C)

Fig 4. Gross appearance of adhesiolysis in dogs intraperitoneal adhesion was induced. NC (A) group, SCMC (B) group and PX/SA (C) group.



* $p < 0.05$ compare with NC group
# $p < 0.05$ compare with SCMC group
Fig 7. The mean strength values of the adhesion separation in each group.

Table 2. Postoperative locations of adhesions in dogs 21 after operation (no. of adhesion sites)

Group	Location			
	S-S	S-M	S-O	S-P
NC	4	11	2	2
SCMC	1	7	4	0
PX/SA	3	4	2	1
Total	8	22	8	3

Locations of adhesions : S-S = serosa-serosa ; S-M = serosa-mesentery; S-O = serosa-omentum ; S-PP = serosa-parietal peritoneum.

and undergo combined healing. Placing a barrier between these wounded surfaces should prevent adhesion formation. Formation of adhesions begins during the inflammatory stage of healing, 24 to 48 hours after injury, and fibroblasts continuously proliferate in a period of repair stage.

Adhesion formation (8,16,17,22,23) begins with a fibrin matrix. The cellular elements become conspicuous in the matrix at 1 to 3 days. The matrix was replaced gradually by vascular granulation tissue that includes macrophages, fibroblasts, and giant cells (15). After 4 days, most of the fibrin disappears, macrophages become the predominant leukocyte, and a larger number of fibroblast and associated collagen are present. At day 5, small vascular channels containing endothelial cells are seen, and within the adhesion while collagen deposition and organization advance (12). During the second week, the relatively few cells present are predominantly fibroblasts. Mesothelium (10) often covers well-defined adhesions, which contain blood vessels and connective tissue fibers, including elastin (22).

Therefore, to prevent adhesion formation, a fibrinolytic agent given at the time of operation must have a long biological half-life. Numerous natural and synthetic resorbable barriers have been shown to reduce adhesion formation. Barrier methods are gaining interest because of their efficacy and absence of serious side effects. Their use is based upon the concept of covering the traumatized intra-abdominal areas, thereby preventing direct apposition of surfaces and avoiding fibrin bridge formation between nearby organs (25). Application of a mechanical barrier between the injured peritoneum is a method to prevent adhesion formation. The ideal barrier should be non-reactive, absorbable and easy to use, and it should remain in the lesion site during critical stages of healing. The use of highly viscous solutions or hydrogels such as carboxymethylcellulose, dextran, and hyaluronic acid (33), instilled after surgical procedures has been suggested as antiadhesive barrier methods.

SCMC is an absorbable hemostatic agent that is formed by dissolving pure α-cellulose in an alkaline solvent. While the mechanism of action of sodium carboxymethylcellulose is not known, it is highly viscous and likely to serve as a barrier and lubricant preventing the adherence between adjacent visceral surfaces. It may also inhibit the movement of inflammatory cells and cellular elements during the period of peritoneal repair.

Composed of poloxamer and sodium alginate, PX/SA is a kind of physical barrier materials. Due to the hydrophobic material dissolving property of biocompatable poloxamer, it is widely used in pharmaceutic field. And PEG (polyethylene glycol) in poloxamer is hydrophilic so it prevent cell adhesion and tissue adhesion (27). Alginate is a kind of polysaccharide that forms a gel by cross-linkage with calcium ions. Cross-linkaged alginate is widely used as carrier of drugs or cells due to property of biocompatibility, biodegradability and nontoxicity (20). The PX/SA is thermo-sensitive gel which means sol form in room temperature and transformed into gel form immediately after surgical operation because it is mixed poloxamer which is a kind of bioavailable polymer and alginate in certain rate.

Accordingly we supposed that the PX/SA functions as a physical barrier by separating the serosal surfaces may be beneficial in the treatment of intraperitoneal adhesion related to inflammation and fibrin.

Bleeding is likely to cause a massive extravasation of fibrinogen into the peritoneal cavity. Adhesion formation begins with fibrin deposition within an inflammatory exudate formed over an injured serosal laye r(26).

Our result showed that RBC counts of blood collected after SCMC and PX/SA administration maintained in normal range in all groups. It is a diverse aspect with study of artificially caused wound in rats (28) because abrasion of tissue did not cause serious blood loss. The variation of serum protein concentrations also maintained in normal range and it resembles as result in rats (28). It is considered that abrasion which is artificial adhesion producing method less changes the concentration of the serum protein than electrocautery or incision. The WBC counts were increased and decreased directly. The increasement in early stage means acute inflammation in abdominal cavity and the decrement means recovery in process of time. The fibrinogen concentrations were increased in NC group and SCMC group until day1 after the operation, increased in PX/SA group until day4 after the sur-

gery, and decreased in normal range in all group. Temporary increasement of the values after the surgery was because of the inflammation like change of WBC counts. There were no significancy among the numerical value of groups.

In present study, we performed by using a SCMC and PX/SA. All of the animals in NC group, SCMC group and PX/SA group were admitted for occurrences of adhesions. Values of adhesion formation in PX/SA group was statistically significant reductions in compared with those in SCMC group ($P < 0.05$). In this results, we can consider that PX/SA reduced the incidence and severity of adhesion because of the physical properties of the material; Reduce fibrin deposits by limiting the inflammatory response, facilitate the degradation of fibrin with fibrinolytic stimulators and separate surfaces during the time that the fibrin remains sticky. The results are in agreement with similar studies (30). PX/SA is a temporary proven to reduce the incidence, extent, and severity of adhesions in patients undergoing abdominal laparotomy. It was designed to prevent adhesions by separating traumatized tissue surfaces. When applied to traumatized tissues, PX/SA becomes a gel and remains in place during the critical 7-day healing period. One advantage of PX/SA is its handing characteristics. It is easy to apply.

Therefore we suggest that the poloxamer/sodium alginate mixture was effective on preventing the formation of postoperative small intestinal adhesions in the dog. Further studies about histological analysis are needed to find inflammatory reaction and fibrotic response in adhesive sites.

Acknowledgement

This research was supported by Kyungpook National University Research Fund, 2007.

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개에서 Poloxamer / Sodium Alginate 혼합물의 복강 유착 방지 효과

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요 약 : 이 실험의 목적은 개에서 poloxamer/sodium alginate 혼합물(PX/SA)의 수술 후 복강 유착 방지 효과를 알아보는 것이다. 잡종견 15마리를 무처치군, 2% Sodium carboxymethylcellulose(SCMC)처치군, PX/SA 처치군으로 각각 5마리씩 배치하였다. 유착은 돌창자의 창자간막 대측에 1 × 1 cm 크기로 미세 점상 출혈 찰과상을 일으켜 유도하였다. SCMC 용액은 카테터를 통하여 복강내 주입하였고, PX/SA는 찰과상 부위에 단순히 도포하였다. 수술 전 1일과 수술 후 1일, 4일, 7일, 14일에 정맥에서 혈액을 채취하여 적혈구수, 총백혈구수, 섬유소원농도를 분석하고, 수술 후 21일에 유착정도를 computerized tensiometer를 이용하여 분석하였다. 적혈구수, 총백혈구수, 섬유소원농도는 각 군간에 유의성은 없다. 유착부 분리에 필요한 평균 장력은 무처치군에서 173.05 ± 113.48 gf, SCMC 처치군에서 111.42 ± 38.25 gf, PX/SA 처치군에서 69.00 ± 45.07 gf였다. PX/SA 처치군의 평균 분리 장력이 다른 두 군에 비하여 유의성 있게 낮았다 ($p < 0.05$). 본 실험 결과로 PX/SA는 SCMC용액과 비교하여 복강유착을 감소시키는 것으로 보아 PX/SA를 개에서 복강 수술 후 유착 방지에 적용 가능한 것으로 생각한다.

주요어 : 개, poloxamer/sodium alginate mixture, 복강유착, 인장강도.