

Efficacies of Sodium Carboxymethylcellulose, Oxidized Regenerated Cellulose and Vitamin E in Prevention Against Postoperative Adhesion Formation in Dogs

Jung-eun Kim, Young-sam Kwon and Kwang-ho Jang¹

College of Veterinary Medicine, Kyungpook National University, Daegu 702-701, Korea

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Abstract : This study was performed to compare the efficacy of the sodium carboxymethylcellulose (SCMC), oxidized regenerated cellulose (ORC), and their combination with vitamin E for the prevention of postoperative adhesions in the dog. Twenty five dogs were randomly divided into five groups ; non-treated group (Control Group), SCMC-treated group (SCMC Group), ORC-treated group (ORC Group), vitamin E and SCMC-treated group (SCMC + E Group), and vitamin E and ORC-treated group (ORC + E group). After laparotomy, 5 abrasions were made to induce intraperitoneal adhesions on the surface of the ileal serosa. The adhesions were occurred in serosa to mesentary (37.6%), serosa to serosa (24%), serosa to omentum (8.8%) and serosa to parietal peritoneum (3.2%). The incidences of adhesions were 92%, 84%, 64%, 56% and 68% in Control, SCMC, ORC, SCMC+E and ORC + E Group, respectively. The adhesion scores in SCMC+E Group were significantly lower than those in the other groups ($p < 0.01$). In conclusion, this study showed that oral supplements of vitamin E and intraperitoneal administration of 2% SCMC solution were effective on reducing intraperitoneal adhesions in the dog.

Key words : Intraperitoneal adhesion, SCMC, ORC, vitamin E, dog.

Introduction

Postoperative formation of peritoneal adhesion is a potential complication of abdominal surgery (7,17), and the most common cause of small intestinal obstruction. Adhesions are fibrinous or fibrous bands that form abnormal unions between two or more surfaces that are normally covered with serosa (4).

Sodium carboxymethylcellulose (SCMC) is a substituted polysaccharide that is prepared by reacting sodium monochloracetate with cellulose, and this solution is clear and semigelatinous. 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, but it is not consistently successful in all cases (6,9).

Vitamin E is a lysosomal membrane stabilizer with antiinflammatory properties (21), and Kagoma *et al* (11) demonstrated that large amount of oral vitamin E to mice preoperatively and postoperatively resulted in a decrease in the incidence and degree of adhesion formation.

Oxidized regenerated cellulose (ORC) is one of the most commonly used bioabsorbable topical hemostatic agents and has been increasingly used as an adjuvant for adhesion prevention in general procedures. It was demonstrated that proper application

of oxidized regenerated cellulose together with surgery was more effective than surgical technique alone in preventing adhesions (8,13,16). A combination of SCMC with pharmacological agents could improve efficacy of the barrier and anticoagulants have been used in an attempt to prevent fibrin deposition, it remains, however, unknown whether there is any synergism of SCMC combined with vitamin E, or oxidized regenerated cellulose combined with vitamin E for adhesion reduction.

Therefore, this study was performed to compare the efficacy of SCMC, ORC, and their combination with vitamin E for the prevention of postoperative adhesions in dogs.

Materials and Methods

Experimental animals

Twenty-five mongrel dogs weighing 3.0 ± 1.4 kg were used in this study. They were vaccinated with dewormed with febantel (Rintal[®], Bayer Korea Ltd., Korea) and were provided with food and water daily. All dogs were divided into five groups contained 5 animals, respectively: non-treated group (Control Group), SCMC-treated group (SCMC Group), Surgicel[®]-treated group (ORC Group), vitamin E and SCMC-treated group (SCMC + E Group), and vitamin E and Surgicel[®]-treated group (ORC + E Group).

Preparations of Materials

SCMC was used in a 2% SCMC solution which was pre-

¹Corresponding author.
E-mail : khojang@knu.ac.kr

pared 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.

In this study, D- α -Tocopherol (GRANDPHEROL[®], Yuhan Co., Korea) and Surgicel[®] (Johnson & Johnson Medical Inc., USA) were used as vitamin E and ORC, respectively.

Surgical Procedures

Anesthesia was induced with atropine sulfate (Atropine[®], Dai Han Pharm. Co. Ltd., Korea, 0.05 mg/kg, SC) and xylazine (Rompun[®], Bayer Korea Ltd., Korea, 1.1 mg/kg, IM) followed by ketamine HCl (Ketamin[®], Yuhan Co., Korea, 22 mg/kg, IM). A 5 cm ventral midline incision was made through the skin, subcutaneous tissue, and peritoneum. After the abdomen was opened, the ileum and ileocecal junction were exteriorized. Total five antimesenteric serosal defects were made in order to induce adhesions by light scraping about 1 × 1 cm areas with a sterile No. 10 scalpel blade to promote petechial bleeding approximately 3 cm from the ileocecal junction and were allowed to air dry for 15 minutes. In Control group, none of adjuvant solutions were instilled into the peritoneal cavity. In SCMC Group, 7 ml/kg of 2% SCMC solution was infused through a catheter before abdominal closure. In ORC group, animals had a sterile 3 × 3 cm patch of ORC placed directly over the lesions. After application, if the ORC fabric turned brown or brown-black color, the piece of ORC was removed by sucking with the oozing blood of the lesion, and a new piece of ORC was placed. In SCMC + E Group, oral supplements of vitamin E (D- α -tocopherol) were administered in doses of 400 IU/day for 5 days before and 14 days after surgery, with intraperitoneal administration of 2% SCMC solution as same method in SCMC Group. In ORC + E Group, ORC was applied at the serosal surface and 400 IU/day of oral vitamin E was administered, as same method in SCMC + E

Group. Then the ileum was replaced in normal position. The abdominal wall was closed.

Postoperative evaluations

Postoperatively, antibiotics (Baytril[®], Bayer Korea Ltd., Korea, 5 mg/kg/day, SC) were administered for 3 days. On preoperative day, 1, 2, 3, and 10, venous blood specimens were collected from all animals for hematologic and biochemical analysis; WBC, RBC, PCV, fibrinogen, AST, ALT, BUN and creatinine. Three weeks later, adhesions were identified, counted, and graded through laparotomy. The grade of the adhesions were evaluated according to the scale: grade 0, no adhesions; grade 1, moderate force required for separation, filmy and/or thin adhesion; grade 2, sharp dissection needed for separation, dense and/or broad adhesion. A total score in each animal was obtained by sum of individual scores to each adhesion.

Statistics

Hematological, biochemical evaluations and severities of adhesions among the control group and the treatment groups were analyzed to see significant differences using analysis of variance (ANOVA) and student-*t* test.

Results

Laboratory Findings

WBC

The changes of WBC values were increased slightly on day 1 and recovered to normal ranges 3 days later in all groups (Table 1).

RBC

The ranges of RBC counts were normal during experiment in all groups (Table 2).

Table 1. Changes of total WBC counts of blood in artificially adhesion-induced dogs (Mean \pm SD, 10³/ μ l)

	Control	SCMC	ORC	Vitamin E & SCMC	Vitamin E & ORC
Pre-operation	11.08 \pm 4.54	11.84 \pm 1.64	10.99 \pm 4.83	9.33 \pm 3.73	8.48 \pm 1.59
day 1	16.33 \pm 7.41	20.64 \pm 5.23	18.62 \pm 2.59	20.60 \pm 6.64	20.91 \pm 3.19
day 2	13.59 \pm 4.69	16.41 \pm 1.80	14.85 \pm 4.08	13.58 \pm 3.38	18.50 \pm 4.81
day 3	9.47 \pm 0.76	15.01 \pm 2.86	13.77 \pm 4.46	11.42 \pm 4.44	10.72 \pm 1.31
day 10	9.18 \pm 0.75	10.06 \pm 0.71	9.14 \pm 0.62	10.56 \pm 2.83	10.10 \pm 0.41

Table 2. Changes of total RBC counts of blood in artificially adhesion-induced dogs (Mean \pm SD, 10⁶/ μ l)

	Control	SCMC	ORC	Vitamin E & SCMC	Vitamin E & ORC
Pre-operation	5.47 \pm 0.45	6.04 \pm 0.47	5.40 \pm 0.34	4.67 \pm 0.50	5.86 \pm 0.60
day 1	5.13 \pm 0.67	5.66 \pm 0.29	5.38 \pm 0.33	4.38 \pm 0.87	5.78 \pm 0.62
day 2	5.31 \pm 0.23	5.48 \pm 0.63	5.25 \pm 0.06	5.91 \pm 0.26	5.33 \pm 0.77
day 3	5.34 \pm 0.15	5.60 \pm 0.46	5.23 \pm 0.10	6.02 \pm 0.20	5.58 \pm 0.46
day 10	5.30 \pm 0.22	5.68 \pm 0.39	5.23 \pm 0.02	5.80 \pm 0.14	5.57 \pm 0.37

Table 3. Changes of total PCV of blood in artificially adhesion-induced dogs (Mean \pm SD, %)

	Control	SCMC	ORC	Vitamin E & SCMC	Vitamin E & ORC
Pre-operation	43.40 \pm 1.67	41.40 \pm 4.83	38.40 \pm 2.97	34.80 \pm 3.70	41.20 \pm 3.83
day 1	41.20 \pm 1.10	41.00 \pm 5.05	42.60 \pm 6.02	36.20 \pm 2.17	36.60 \pm 1.95
day 2	41.40 \pm 1.34	36.00 \pm 6.52	41.40 \pm 4.34	39.40 \pm 5.64	36.60 \pm 4.00
day 3	42.40 \pm 1.34	37.40 \pm 7.60	34.60 \pm 3.71	32.20 \pm 2.17	33.80 \pm 4.92
day 10	42.60 \pm 0.55	35.40 \pm 3.85	38.00 \pm 2.00	33.20 \pm 3.11	32.60 \pm 3.71

Table 4. Changes of total fibrinogen concentrations of blood in artificially adhesion-induced dogs (Mean \pm SD, mg/dl)

	Control	SCMC	ORC	Vitamin E & SCMC	Vitamin E & ORC
Pre-operation	212.00 \pm 18.87	221.20 \pm 79.75	380.60 \pm 107.04	202.60 \pm 25.09	302.80 \pm 24.85
day 1	351.20 \pm 100.21	314.60 \pm 106.47	499.60 \pm 100.47	247.00 \pm 27.72	453.20 \pm 39.46
day 2	453.20 \pm 55.58	350.20 \pm 35.95	392.80 \pm 63.79	429.60 \pm 66.76	403.00 \pm 59.75
day 3	441.40 \pm 32.64	398.60 \pm 31.56	440.20 \pm 64.60	409.60 \pm 44.87	368.20 \pm 68.04
day 10	338.60 \pm 95.43	328.40 \pm 160.74	314.80 \pm 123.19	389.20 \pm 79.44	372.60 \pm 110.75

PCV

The values showed no significant differences among groups (Table 3).

Fibrinogen

The fibrinogen changes showed no statistical significances among groups (Table 4).

Blood biochemistry

Plasma ALT, AST, BUN and creatinine values had no significant statistical differences among control groups and the treated groups.

Assessments of adhesions

Three weeks after induction of peritoneal adhesions, the peritoneums were inspected for the locations (Table 5), incidences (Fig 1) and degrees (Table 6) of adhesions. All of animals were admitted for occurrences of adhesions. Adhesions were identified in total sites; serosa to mesentery (47 of 125, 37.6%),

Table 5. Postoperative locations of adhesions in ileum of dogs on day 21 after operation

	Location*			
	S-S	S-M	S-O	S-PP
Control	7	11	4	1
SCMC	3	10	6	2
ORC	2	14	-	-
Vitamin E & SCMC	6	8	-	-
Vitamin E & ORC	12	4	1	1

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

serosa to serosa (30 of 125, 24%), serosa to omentum (11 of 125, 8.8%), serosa to parietal peritoneum (4 of 125, 3.2%).

The adhesions were developed at 23 of 25 sites (92%), 21 of 25 (84%), 16 of 25 (64%), 14 of 25 (56%), and 17 of 25 (68%) in Control, SCMC, ORC, SCMC + E, and ORC + E Group, respectively (Fig 1).

The adhesion score was 9 ± 1.73 , 6 ± 3.16 , 7 ± 2.74 , 3.2 ± 0.84 ($p < 0.05$), and 4 ± 1.87 ($p < 0.05$) in Control, SCMC, ORC, SCMC + E, and ORC + E Group, respectively (Table 6). The incidence and scores of adhesion were lowest in the SCMC + E Group.

Discussion

A recent study using dietary vitamin E supplement showed a significant reduction in postoperative peritoneal adhesions in mice (11,21). Previous studies by Hemadeh *et al* (10) showed that there was 50% fewer significant adhesions in the group that received oral supplements of vitamin E (30 IU/kg/day). This reduction could be due to the important role of vitamin E in maintaining the stability of cellular elements (platelets) and organelle membranes, particularly the lysosomal membranes (15). In addition to stabilizing platelet membranes, vitamin E may have an effect on platelet aggregation (20). The exact

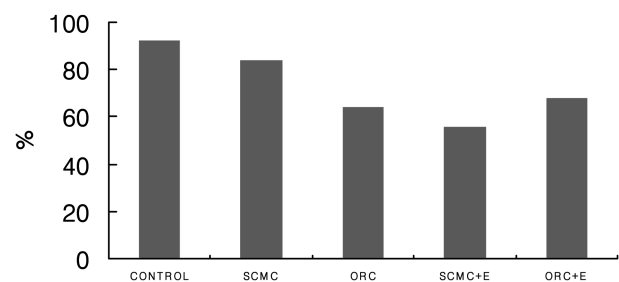
**Fig 1.** Adhesion incidences in dogs on day 21 after operation.

Table 6. Postoperative adhesion scores in dogs on day 21 after operation

Groups	No. of dogs used	Total adhesion score	
		Individual score	Median (Mean \pm SD)
Control	1	9	9 \pm 1.73
	2	6	
	3	10	
	4	10	
	5	10	
SCMC	1	4	6 \pm 3.16
	2	6	
	3	10	
	4	2	
	5	8	
ORC	1	6	7 \pm 2.74
	2	7	
	3	3	
	4	9	
	5	10	
SCMC + E	1	3	3.2 \pm 0.84*
	2	4	
	3	2	
	4	4	
	5	3	
ORC + E	1	2	4 \pm 1.87*
	2	2	
	3	5	
	4	5	
	5	6	

*SCMC + E and ORC + E group ; $p < 0.05$ compared with control group

mechanism of action on wound-healing is not known. If supplemental vitamin E diminishes platelet aggregation and thrombus formation, it may decrease the amount of fibroblasts and smooth-muscle mitogens released by activated platelets (12). As a consequence, it eventually lead to a prevention of adhesion formation. Vitamin E has shown to have similar effects on wound healing, collagen formation and fibroblast proliferation when compared with glucocorticoids, without untoward side effects (21). Previous animal studies showed that the toxicity of vitamin E is low and that the vitamin E is not mutagenic, carcinogenic, or teratogenic (1). In this study, supplemental vitamin E for adhesion prevention didn't cause any toxic effects when administered to dogs in dosages 400 IU/day during experimental periods. Also, since it does not result in the severe immunosuppression and other side effects associated with glucocorticoids, supplemental vitamin E may offer an attractive means to decrease the incidence and degree of peritoneal adhesions effectively. Hemadeh *et al* (10) described that

there were no significant differences in adhesion formation among various vitamin E dose, but they appear to be equally effective when combined with SCMC. The significant reduction in postoperative adhesion (90%) in group using vitamin E combined with SCMC appear to be the result of a synergistic effect between oral supplements of vitamin E and the intraperitoneal administration of SCMC solution (10).

ORC is an adhesion barrier approved for use to prevent postoperative adhesions. Its mechanism of action is unknown, but it has been considered to function as a physical barrier. Larsson *et al* (14) first suggested that a knitted fabric made of this material might be a promising agent in the prevention of cecal adhesions. Mais *et al* (8) found it prevented peritoneal adhesion formation in human. When compared with untreated controls, oxidized regenerated cellulose significantly more reduced postoperative adhesion formation to the lateral abdominal sidewall of rabbits (18). No complications from the use of the ORC were reported by Diamond MD *et al* (5) and the fabric was known to form a gelatinous mass in 1 to 4 days and to dissolve completely in approximately 10 to 14 days. In this study, when the abdomen was reopened on day 21 after laparotomy, the ORC absolutely dissolved and all dogs of ORC Group and ORC + E Group did not appear to have any complications. No adverse events were recorded in ORC Group during the study. At second-look laparoscopy, no residual material was observed, no tissue reactions were noted, and no evidences of tissue damage in adjacent structures were found in this group.

In this study, WBC account was recorded high level on day 1 after laparotomy and then gradually reduced near the normal range. Other hematological and biochemistry values remained generally within normal ranges. It was thought as a result of acute inflammatory reaction for induction intraperitoneal adhesion as reported in rats (3) and dogs (2) model. Singer *et al* (19) demonstrated that frequencies of adhesion formation were serosa to serosa (65.8%), serosa to mesentery (26.2%), serosa to omentum (5.4%) and serosa to incision sites (2.4%), but adhesion formation was not occurred in serosa to parietal peritoneum. In present study, the frequencies of adhesion formations were serosa to mesentery (47/125, 37.6%), serosa to serosa (30/125, 24%), serosa to omentum (11/125, 8.8%) and serosa to parietal peritoneum (4/125, 3.2%). It had a somewhat similar result to previous study. In present study, SCMC + E Group (3.2 \pm 0.84), and ORC + E Group (4 \pm 1.87) were found to be significantly lower adhesion formation than in Control Group (9 \pm 1.73), SCMC Group (6 \pm 3.16) and ORC Group (7 \pm 2.74) on adhesion prevention. The most favorable adhesion prevention was achieved in SCMC + E Group in comparison with ORC + E Group. The exact mechanism for synergistic beneficial effect of oral supplements of vitamin E and the intraperitoneal administration of SCMC solution in reducing the intraperitoneal adhesions is not known. However, the significant reduction in postoperative adhesions in SCMC + E Group appears to be a synergistic effect between oral supplements of vitamin E and the intraperitoneal administration of SCMC solution.

Conclusion

It could be concluded that oral supplements of vitamin E and intraperitoneal administration of 2% SCMC solution might be significantly effective in reducing intraperitoneal adhesions in dogs.

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개에서 복강수술 후 유착방지에 대한 Sodium carboxymethylcellulose, Oxidized regenerated cellulose, Vitamin E의 효과

김정은 · 권영삼 · 장광호¹

경북대학교 수의과대학

요 약 : 개에서 복강수술 후 유착방지에 대한 sodium carboxymethylcellulose (SCMC), oxidized regenerated cellulose (ORC), vitamin E의 병용효과를 알아보기로 본 실험을 수행하였다. 실험견은 대조군, SCMC 처치군, ORC 처치군, SCMC와 vitamin E 처치군, ORC와 vitamin E 처치군의 5개군으로 분류하고 각 군에 5두씩 배치하였다. 정중개복 후 회장 장막에 6 cm 간격으로 5곳에 찰과상을 입혀 유착을 유발했다. 유착장소는 전군에서 장막-장간막(37.6%), 장막-장막(24%), 장막-대망막(8.8%), 장막-복막(3.2%) 순으로 발생하였다. 유착발생빈도는 SCMC와 vitamin E 처치군이 56%로 대조군 92%, SCMC 처치군 84%, ORC 처치군 64%, ORC와 vitamin E 처치군 68%에 비해 낮았다. 유착형성 점수는 SCMC와 vitamin E 처치군에서 다른 처치군에 비해 유의적인 감소를 나타내었다($p < 0.01$). 따라서, 복강수술 후 유착방지에 있어 SCMC와 vitamin E의 병용이 개에서 효과적이라고 생각된다.

주요어 : 개, 복강유착, SCMC, ORC, vitamin E