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The Effect of Hyaluronic Acid and Vitamin E Combination on Preventing Postoperative Intraperitoneal Adhesion Formation in Dogs

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Abstract : This study was performed to compare the effect of hyaluronic acid(HA), vitamin E and their combinations for the prevention of postoperative intraperitoneal adhesion in dogs. Twelve mongrel dogs were divided into four groups; HA- (HA Group), vitamin E 800IU- (E8 Group), HA + vitamin E 800IU- (HA+E8 Group) and HA + vitamin E 1600IU-treated group(HA+E16 Group) with three dogs in each group. After celiotomy, five abrasions of 1× 1 cm area were made on the antimesenteric serosal surface of the anterior ileocecum with a No. 10 scalpel blade. The five abrasions and peritoneal cavity were coated with 25 of 0.1% HA. Oral supplements of vitamin E were given from the fifth day before the operation to the fourteenth day after the operation. Hematologic values were evaluated before the operation and on the 1st, 4th, 7th and 14th day after the operation. The locations and scores of adhesion were assessed through the second operation on the 21st day after the first operation. The adhesions were located on serosa to mesentary(43.3%), serosa to serosa(20%), serosa to omentum(5%) and serosa to parietal peritoneum(1.7%). The incidences of adhesion in HA, E8, HA+E8 and HA+E16 groups were 80%, 100%, 47% and 53%, respectively. The scores of adhesion in HA+E8 group($p < 0.05$) were lower than those in other groups. This study showed that the combination of HA and vitamin E 800IU was significantly effective in reducing the intraperitoneal adhesion in dogs.

Key words **:** hyaluronic acid, vitamin E, adhesion, celiotomy, dog

Introduction

Postoperative adhesion formation is a major challenge in abdominal surgery, as it is the main cause of many pathological states, including obstruction, infertility, and others[1]. Adhesions are fibrinous or fibrous bands that form abnormal unions between two or more surfaces that are normally covered with serosa[2]. The pathogenesis of adhesion formation has been described as a fibroproliferative response of the mesothelial tissue following peritoneal injury involving humoral mechanisms as well as cell to cell relationship[1,3].

Numerous studies have been done to prevent or reduce the complication of intraperitoneal adhesions in animals. Historically, these treatment fall into five categories, first described by Boys[4] in 1942 as the "five fundamental attacks directed towards the prevention of adhesions" ; 1) to limit or prevent initial peritoneal injury, 2) to remove or dissolve the deposited fibrin, 3) to keep apart the fibrin-coated peritoneal surfaces until mesothelialization has occurred, 4) to inhibit fibroblastic proliferation, and 5) to prevent coagulation of the serous exudate.

Recent efforts to lower the incidence of adhesion formation have been focused on a barrier and a fibrinolytic agent. Hyaluronic acid(HA) is a linear polysaccharide comprised of alternating glucosamine residues that interact with other proteoglycans to provide stability and elasticity to the extracellular matrix of all tissues[5]. HA is a high-weight polysaccharide found through mammalian tissues and is an important component of the extracellular matrix involved in tissue repair[9]. HA has been known as playing a role in normal wound healing[5,6] and in inhibiting peritoneal[7-11], pericardial[12] adhesion formation. Especially HA acts as a barrier to separate damaged tissue surfaces during the critical phases of peritoneal wound repair and was associated with a significant reduction in postoprative intraperitoneal adhesions.

Vitamin E was first discovered in 1936. There are several naturally occurring tocopherols, and D-α-Tocopherol has the widest natural distribution and the greatest biologic activity. In 1967 Stuyvesant *et al*[13] reported it to be a lysosomal membrane stabilizer with antiinflammatory properties, and then Ehrleich and co-workers[14] had showed that intramuscular vitamin E administerd postoperatively inhibited collagen formation in wounds and had effects similar to those of corticosteroids on wound healing and fibroblast activity. Kagoma *et al*[15] 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.

Therefore, the purpose of this study was to compare the effect of hyaluronic acid(HA), vitamin E and their combinations for the prevention of postoperative intraperitoneal adhesion in dogs.

Materials and Methods

Experimental Animals

Twelves dogs weighing 3.5±0.2 were used in this study. They were vaccinated with DHPPL, dewormed with febantel

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(Rintal®, Bayer Korea Ltd., Korea). Experiments were started after an initial adaption for about two weeks. The experimental animals were randomly divided into four groups; HA- (HA Group), vitamin E 800IU- (E8 Group), HA + vitamin E 800IU- (HA+E8 Group) and HA + vitamin E 1600IU-treated group(HA+E16 Group). Three dogs were allocated to each group.

Preparation of Materials

Hyaluronic acid(HA) was used in a 0.1% HA solution. It was prepared by adding 22.5 ml of sterile water at 1% HA (Sodium hyaluronate 25 mg/2.5 ml, HYAL®, Shinpoong Pharm. Co., Korea) and then mixing with Vortex Genie 2, filtering with syringe filter(0.45 Micron, 25 mm). It was stored at 4°C before usage.

The vitamin E (D-α-Tocopherol, GRANDPHEROL®, Yuhan Co., Korea) was administered per oral.

Surgical Procedures

Food was withheld from experimental dogs for twelves hours prior to surgery. The dogs were anesthetized with 0.05 mg/kg of atropine sulfate subcutaneously(Atropine®, Dai Han Pharm. Co. Ltd., Korea) and 1.1 mg/kg of xylazine intramuscularly(Rompun®, Bayer Korea Ltd., Korea) followed by 22 mg/kg of ketamine HCl intramuscularly(Ketamin®, Yuhan Co., Korea). The dogs were placed in dorsal recumbency and the entire abdomen was clipped. The abdominal skin was prepared with povidone-iodine solution and 70% alcohol for aseptic surgery, sterile surgical instruments and supplies were used in all surgical procedures. Routine midline celiotomy was performed beginning umbilical cord and extending caudally 5 cm in length. After the abdomen was opened, ileocecal junction was identified, total five distinct surgical abrasions were made in order to induce adhesions. The antimesenteric abrasion of the ileum approximately 10 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(Fig 1A) The total abrasions were 5 places at intervals of 5 cm (Fig 1B) One abrasion was coated with 3 ml of 0.1% HA solution followed by 15 minutes of air drying. The total coated volume is 15 ml of 0.1% HA. The abrasions were dropped back into the abdomen and 3 ml of 0.1% HA solution/kg was administered through the catheter, using a sterile syringe over a entire peritoneal cavity, before closure.(Fig 1C) Therefore, the five abrasions and peritoneal cavity were coated with 25 ml of 0.1% HA. The peritoneum was closed using a simple continuous suture of 2-0 catgut and the skin was closed by a simple interrupted suture of 3-0 nylon.

Oral supplements of vitamin E were administerd in dose of 800, 1600 IU/day from the fifth day before the operation to the fourteenth day after the operation.

Postoperative Evaluations

Each animal was monitored daily for signs of abdominal pain, incisional swelling or drainage, food consumption or defecation. Antibiotics(Baytril®, Bayer Korea Ltd., Korea, 5 mg/kg/day) were administered subcutaneously to reduce the risk of postoperative infection for three days.

The locations and scores of adhesion were assessed through the second operation on the 21st day after the first operation. A total score in each animal was obtained by sum of individual scores to each adhesion. The adhesion grade was determined according to modified Heidrick *et al*[16] : grade 0 = no adhesion; grade 1 = moderate force required for separation, filmy and/or thin adhesion; grade 2 = sharp dissection needed for separation, dense and/or broad adhesion.

On preoperative day, 1st, 4th, 7th, and 14th, venous blood specimens were collected from all experimental animals for hematologic and biochemical analysis : WBC, RBC, PCV, fibrinogen, AST, ALT, BUN and creatinine.

Statistical Analysis

All data are expressed as mean±standard deviation. Hematological, biochemical evaluations and severities of adhesions were analyzed to see significant differences using analysis of variance(ANOVA) and student's *t*-test.

Fig 1. Surgical procedures for evaluating intestinal adhesions. A, The antimesenteric abrasion of the ileum was created by light scraping about 1×1 cm areas with a sterile No. 10 scalpel blade to promote petechial bleeding. B, The total abrasions were 5 places at intervals of 5 cm. C, 0.1% HA solution was administered through the catheter.

Results

Laboratory Findings

WBC. The change of WBC values(10^3/μl) were increased from 10.01±2.20 on pre-operation to 26.91±7.29 on day 1 in HA Group, from 10.25±4.42 to 23.00±6.26 in E8 Group, from 14.50±4.75 to 19.10±1.09 in HA + E8 Group and from 16.35±5.20 to 31.85±7.60 in HA + E16 Group. The WBC values of HA, E8, HA + E8 and HA + E16 were 9.71 ±4.51, 13.71±5.85, 12.75±1.40 and 14.88±1.62 on day 14, respectively. These values decreased gradually from day 4, and recovered from normal ranges on day 14(Table 1).

RBC. The ranges of RBC counts(10^6/μl) were from 5.35 ±0.97 to 6.31±0.97 in HA Group, from 4.81±0.72 to 6.57±1.93 in E8 Group, from 4.80±0.41 to 6.21±0.59 in HA + E8 Group and from 5.10±0.65 to 5.75±1.85 in HA + E16 group. The values showed no significant differences among the Groups(Table 2).

PCV. The PCV values(%) were from 42.33±3.51 to 46.67±7.23 in HA Group, from 35.00±8.66 to 42.67±3.21 in E8 Group, from 36.33±8.02 to 41.33±9.61 in HA+E8 Group and from 37.67±6.35 to 42.33±4.93 in HA+E16 Group. The values showed no significant differences among the Groups(Table 3).

Fibrinogen. The changes of fibrinogen values(mg/dl) were increased from 240.33±99.36 on pre-operation day to 386.67±49.37 on day 1 in HA Group, from 197.50±41.50 to 291.50±42.50 in E8 Group, from 285.75±38.25 to 357.50±122.50 in HA+E8 Group and from 279.33±81.51 to 513.40±137.60 in HA+E16 Group. The fibrinogen values of HA, E8, HA+E8 and HA+E16 were 208.50± 152.50, 225.00±72.00, 199.23±29.23 and 271.50±38.50 on day 7, respectively. These values decreased gradually from day 4, and recovered from pre-operation ranges on day 7. The values showed no significant differences among the Groups(Table 4).

Table 1. Changes of total WBC counts of blood after operation in dogs (Mean±SD, 10^3/μl)

Day	HA*	E8	HA + E8	HA + E16
Pre-operation	10.01±2.20	10.25±4.42	14.50±4.75	16.35±5.20
1	26.91±7.29	23.00±6.26	19.10±1.09	31.85±7.60
4	16.06±3.47	17.26±3.75	13.55±5.95	17.26±8.83
7	14.53±4.56	15.16±5.15	14.95±5.39	16.15±2.05
14	9.71±4.51	13.71±5.85	12.75±1.40	14.88±1.62

*HA(Hyaluronic acid), E8(vitamin E 800IU), HA+E8(HA + vitamin E 800IU) and HA+E16(HA + vitamin E 1600IU)-treated groups.

Table 2. Changes of total RBC counts of blood after operation in dogs (Mean±SD, 10^6/)

Day	HA	E8	HA + E8	HA + E16
Pre-operation	6.31±0.97	6.57±1.93	6.21±0.59	5.42±0.68
1	5.35±0.97	6.00±1.08	5.29±0.25	5.68±1.35
4	5.84±0.60	5.79±0.46	5.14±1.17	5.10±0.65
7	5.49±0.37	4.81±0.72	4.80±0.41	5.75±1.85
14	5.70±0.55	5.53±0.92	4.91±0.31	5.57±1.91

Table 3. Changes of total PCV of blood after operation in dogs (Mean±SD, %)

Day	HA	E8	HA + E8	HA + E16
Pre-operation	46.67±7.23	42.67±3.21	41.33±9.61	42.33±4.93
1	44.67±9.07	41.33±2.31	39.00±8.89	42.33±8.02
4	42.33±3.51	35.00±8.66	36.33±8.02	38.00±6.08
7	44.00±6.08	38.11±2.52	38.17±7.64	37.67±6.35
14	46.00±6.56	39.33±1.15	39.67±6.66	37.67±6.35

Table 4. Changes of total fibrinogen concentrations of blood after operation in dogs (Mean±SD, mg/dl)

Day	HA	E8	HA + E8	HA + E16
Pre-operation	240.33± 99.36	197.50±41.50	285.75± 38.25	279.33± 81.51
1	386.67± 49.37	291.50±42.50	357.50±122.50	513.40±137.60
4	249.00± 53.00	229.00±33.00	212.55± 47.55	334.00± 12.00
7	208.50±152.50	225.00±72.00	199.23± 29.23	271.50± 38.50
14	218.00± 97.86	156.00±16.00	254.50± 55.50	273.00± 70.93

Blood Biochemistry. Plasma ALT, AST, BUN and Creatinine values had no significant statistical differences among the groups. The values were remained normally during experiment period.

Assessments of Adhesions

The adhesion grade was determined according to previous study[16]: grade 0 = no adhesion; grade 1 = moderate force required for separation, filmy and/or thin adhesion; grade 2 = sharp dissection needed for separation, dense and/or broad adhesion(Fig 2).

Adhesions were identified in total sites; serosa to mesentery (26 of 60, 43.3%), serosa to serosa(12 of 60, 20%), serosa to omentum(3 of 60, 5%) and serosa to parietal peritoneum (1 of 60, 1.7%). The incidences of adhesion in HA, E8, HA+E8 and HA+E16 groups were 80%, 100%, 47% and 53%, respectively(Table 5, Fig 3).

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

Group	Locations of adhesion*			
	S-S	S-M	S-O	S-PP
HA	4	6	1	1
E8	4	10	1	-
HA+E8	-	6	1	-
HA+E16	4	4	-	-

*Locations of adhesion, S-S; serosa-serosa, S-M; serosa-mesentery, S-O; serosa-omentum, S-PP; serosa-parietal peritoneum

HA Group- Moderate to severe adhesions were developed in 12 of the 15(80%) induced peritoneal adhesion sites, and adhesion score is 5.3±0.58.

E8 Group- The most severe adhesions were developed in 15 of the 15(100%) induced peritoneal adhesion sites, and adhesion score is 7±1.00.

HA+E8 Group- Moderate adhesions were developed in 7 of the 15(46.6%) induced peritoneal adhesions sites, and adhesion score is 2.3±1.15. There was statistically most significant reduction as compare with extents and degrees of HA and E8 Group in adhesion formation($p < 0.05$).

HA+E16 Group- Moderate adhesions were developed 8 of the 15(53.3%) induced peritoneal adhesions sites, and adhesion score is 3±1.00. There were significant reduction in adhesions in comparison to HA and E8 Group, but statistical significance was not reached(Table 6).

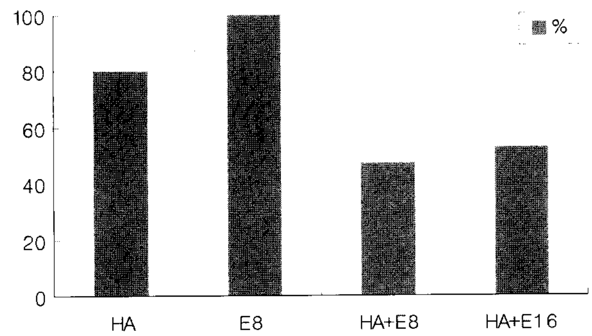

Fig 3. Adhesion incidences in dogs on day 21 after operation

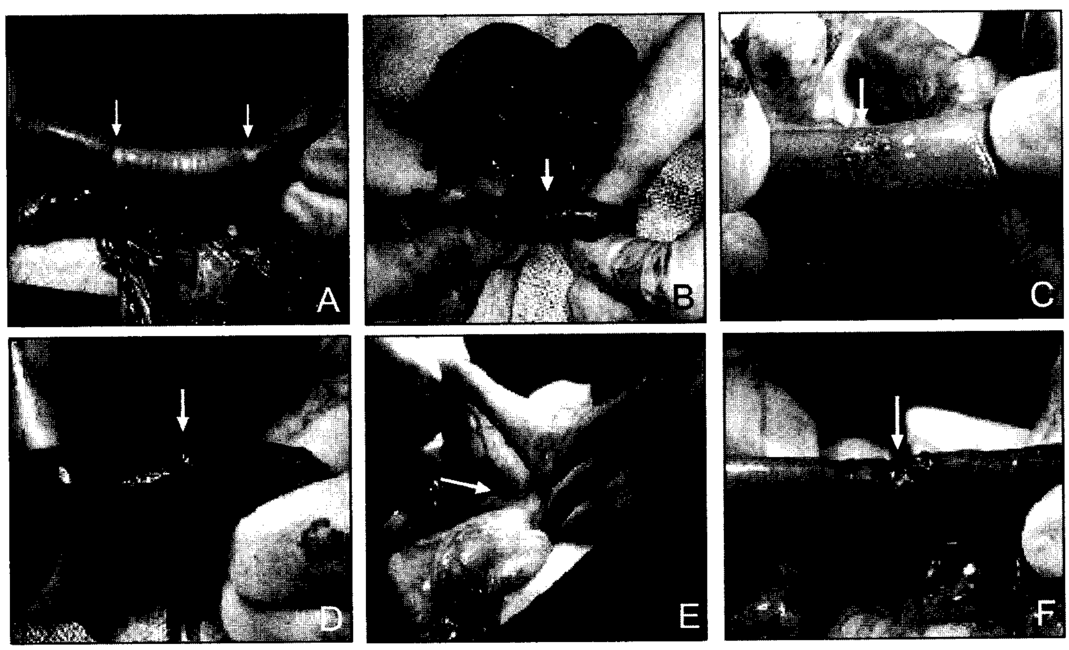

Fig 2. Second celiotomy on day 21 after the first operation for evaluating the locations and scores of adhesions. A, B; Arrows indicate no adhesion(Grade 0), C; Arrows indicate filmy and/or thin adhesion(Grade 1), D; The adhesions were separated by moderate force(Grade 1), E; Arrows indicate dense and/or broad adhesion(Grade 2), F; The adhesions were separated by sharp dissection of scalpel blade(Grade 2).

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

Groups	No. of dogs used	Total adhesion score	
		Individual score	Mean±SD
HA	1	5	5.33±0.58
	2	6	
	3	5	
E8	1	8	7±1.00
	2	6	
	3	7	
HA+E8	1	3	2.33±1.15*
	2	3	
	3	1	
HA+E16	1	2	3±1.00
	2	3	
	3	4	

*$p < 0.05$ compared with HA, E8 Group

Discussion

Tissue injury occurs normally in all surgical procedures by direct injury at sites of cutting, suturing, handling, etc., or by indirect injury at adjacent sites in the surgical field from desiccation, thermal injury, or abrasive manipulations[17,18]. Injury to the peritoneum leads to the formation of a fibrinous exudate. Fibrin exudes from peritoneal mesothelial cells, and most of them is lysed and absorbed. Body defenses most often resolve the fibrinous strands via phagocytosis and enzyme digestion. However, the defense fails if the injury involves a fairly large area or if there is low concentration of enzymes and leukocytes, and result in performing permanent fibrinous adhesions[19]. Subsequently, if these fibrinous adhesions are not lysed, they are organized into fibrous adhesions by synthesis of pathological connective tissue by activated fibroblasts.

The clinical consequences of these adhesions are serious. Innumerable substances and methods have been used, either locally in the peritoneal cavity or systematically, for an effect to prevent or reduce the occurrence of postoperative peritoneal adhesions. This may either reduce the amount of exudate, prevent its coagulation, reduce contact between surfaces, remove fibrin after its apperance or stop proliferation of fibroblasts[19]. Recent efforts to lower the incidence of adhesion formation have been focused on a barrier and a fibrinolytic agent.

Hyaluronic acid(HA) is a linear polysaccharide comprised of alternating glucosamine residues. HA has been shown to affect macropahges and fibroblast activity[2,20,21] most probably through the HA receptor CD44, which has been shown to be expressed on fibroblasts and macrophages. Alexander *et al*[22] suggested that HA may reduce the formation of postsurgical adhesions at early postsurgical points. HA is a high-weight polysaccharide found through mammalian tissues. In the present study, aqueous solutions of biocompatible anionic polysaccharides were used at the beginning of and during a model cardiac surgical procedure to inhibit pericardial injury due to abrasion and desiccation which would initiate adhesion formation. This approach to adhesion prevention is different from methods which employ barrier fluids or films interposed between the injured epicardium and the sternum to physically block formation of adhesions between those two structures. Previous work by other investigators have shown the effectiveness of this approach in preventing abdominal[23-26], pelvic[27], and pericardial[12] adhesion in animals. These studies have shown that effective adhesion prevention is achieved if the tissues are coated with the polymer solutions prior to desiccation and with periodic coating of tissues with the polymer solutions during prolonged procedures. Use of these dilute low-viscosity solutions at the conclusion of surgery alone is not effective because they do not function as good physical barriers to maintain separation of injured tissue during the healing process[27-31]. Large volumes of concentrated and very viscous solutions may be more effective for use at the conclusion of surgery, but this remains to be examined.

Vitamin E is a fat-soluble vitamin found in the diet, such as vegetable oils, cereal grains, green plants, egg yolk, milk fat, liver and nuts. Vitamin E is a generic name for a group of tocol and tocotrienol derivatives that have some degree of vitamin activity, and α-Tocopherol is considered to be the most active form[32]. Data from animal studies showed that the toxicity of vitamin E is low and that the vitamin is not mutagenic, carcinogenic, or teratogenic[32]. Few side effects have been reported, even at doses as high as 3200 IU/day in human[32]. In this study, supplemental vitamin E for adhesion prevention caused no apparent toxic effects when administered to dogs in dosages 800, 1600 IU/day during experimental periods. A recent study using dietary vitamin E supplement showed a significant reduction in postoperative peritoneal adhesions in mice[15,33]. Previous studies by Hemadh *et al*[33] showed that 50% fewer significant adhesions in the group that received oral supplements of vitamin E (30 IU/kg/day). Vitamin E is believed to play an important role in maintaining the integrity of cellular, cellular element(platelet), and organelle membranes, affecting lysosomal membranes in particular[34]. At the molecular level, fat-soluble vitamin E is highly concentrated in membranes where it serves as a scavenger of locally generated free radicals such as superoxides, peroxides, and hydroxyl radicals[35]. Furthermore, vitamin E has been shown to inhibit platelet serotonin release, platelet aggregations[36-38]. These events may lead to a reduction in thromboplastin and fibrin generation[39]. Considering the role of fibrin in the formation of adhesions[40], this may be another mechanism by which vitamin E reduces postoperative adhesion formation.

In summary, HA solution have been demonstrated to be effective in inhibiting the formation of postoperative adhesions in a clinically relevant canine intraperitoneal adhesion model. From this study and others, the mechanism by which tissue coating with aqueous solutions of anionic polysaccharides reduces peritoneal adhesion formation appears clearly related to the protection of fragile serosal surfaces (i.e., methothelium) from abrasive and desiccation trauma during surgery. This solutions perform as temporary tissue-protective devices rather than as physical barriers to the formation of connective tissue between wounded surfaces. The significant reduction in postoperative adhesion in group using vitamin E combined with HA appear to be the result of synergistic effect between oral supplements of vitamin E and HA solution.

In short, this study showed that the combination of HA and vitamin E 800 IU was significantly effective in reducing the intraperitoneal adhesion in dogs.

References

1. Crowe DT Jr, Bjorling DE. Peritoneum and peritoneal cavity. In: Textbook of small animal surgery, 2nd ed. Philadelphia: WB Saunders. 1985: 413-415.
2. Klein ES, Asculai SS. Effects of hyaluronic Acid on fibroblast behavior in peritoneal injury. J Surg Res 1996; 61: 473-476.
3. Cheong J, Lee K, Jang K. Prevention of abdominal re-adhesions by sodium carboxymethylcellulose in dogs with abdominal adhesions. Korea J Vet Clin Med 1997; 14: 161-167.
4. Boys F. The prophylaxis of peritoneal adhesions. a review of the literature. Surgery 1942; 11: 118-168.
5. King SR, Hickersin WL, Proctor KG. Beneficial actions of exogenous hyaluronic acid on wound healing. Surgery 1991; 109: 76-84.
6. Brecht M, Mayer U, Schlosser E, Prehm P. Increased hyaluronate synthesis is required for fibroblast detachment and mitosis. Biochem J 1986; 239: 445-450.
7. Reijnen, Michel MP. Polyanionic polysaccharides reduce intra-abdominal adhesion and abscess formation in a rat peritonitis medel. J Surg Res 2001; 101: 248-253.
8. Thornton, Melvin H, Douglas B. Clinical evaluation of 0.5% ferric hyaluronate adhesion prevention gel for the reduction of adhesions following peritoneal cavity surgery: open-label pilot study. Human Reproduction 1998; 13: 1480-1485.
9. Johns DS, Kiorpes TC, Rodgers KE, DiZerega GS, Donahue WD. Reduction of adhesion formation by postoperative administration of ionically cross-linked hyaluronic acid. Fertil Steril 1997; 68: 37-42.
10. Leach RE, Burns JW, Dawe EJ, SmithBarbour MD, Diamond MP. Reduction of postsurgical adhesion formation in the rabbit uterine horn model with use of hyaluronate/carboxymethylcellulose gel. Fertil Steril 1998; 69: 415-418.
11. Haney AF, Doty E. A barrier composed of chemical cross-linked hyaluronic acid(Incert) reduces postoperative adhesion formation. Fertil Steril 1998; 70: 145-151.
12. Seeger, James M, Kaelin. Prevention of postoperative pericardial adhesions using tissue-protective solution. J urg Res 1997; 68: 63-66.
13. Stuyvesant VW, Jolley W. Anti-inflammatory activity of d-á-Tocopherol vitamin E) and linoleic acid. Nature 1967; 216: 585-586.
14. Ehrleich H, Tarver H, Hunt TK. Inhibitory effect of vitamin E on collagen synthesis and wound repair. Ann Surg 1972; 175: 235-240.
15. Kagoma P, Burger SN, Seifter E, Levenson SM, Demetriou AA. The effect of vitamin E on experimentally induced peritoneal adhesions in mice. Arch Surg 1985; 120: 949-951.
16. Heidrick GW, Pippitt CH, Morgan MA, Thurnau GR. Efficacy of intraperitoneal sodium carboxymethylcellulose in preventing postoperative adhesion formation. J Reprod Med 1994; 39: 575-578.
17. Milligan DW, Raftery AT. Observation on the pathogenesis of peritoneal adhesions : a light and electron microscopical study. Br J Surg 1974; 61: 274-280.
18. Ellis H, Harrison W, Hugh TB. The healing of peritoneum under normal and abdominal conditions. Br J Surg 1965; 52: 471-481.
19. Kapur BML, Talwa JR, Gulati SM. Oxyphenbutazone anti-inflammatory agent in prevention of peritoneal adhesions. Arch Surg 1969; 98: 301-302.
20. Nanaka, Tohgo, Hiraku. Comparison of the inhibitory effects of two types of hyaluronic acid on the expression of fibrinolytic factors in human synovial fibroblasts. Modern Rheuma 2002; 12: 160-166.
21. Isnard N, Legeais JM, Renard G. Effect of hyaluronan on MMP expression and activation. Cell Biology Int 2001; 25: 735-739.
22. Alexander H, 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: 671-689.
23. Yaacobi Y, Israel AA, Goldberg EP. Prevention of postoperative abdominal adhesions by tissue precoating with polymer solutions. J Surg Res 1993; 55: 422-426.
24. Schier F, Danzer M. Hyaluronate, tetrachlorodecaoxide, and galactolipid prevent adhesions after implantation of Gore-Tex and dura mater into the abdominal wall in rats. Pediatr Surg Int 1999; 15: 255-259.
25. Elbert, Donald L. Reduction of fibrous adhesion formation by a copolymer possessing an affinity for anionic surfaces. J Biomed Materials Res 1998; 42: 55-65.
26. Verco, Shelagh JS, DiZerega. Development of a novel glucose polymer solution for adhesion prevention. Human Reproduction 2000; 15: 1764-1772.
27. Elkins TE, Bury RJ, Ahokas RA, Malinark LR. Adhesion prevention by solutions of sodium carboxymethylcellulose in the rat. I. Fertil Steril 1984; 41: 926-928.
28. Dizerega GS. Contemporary adhesion prevention. Fertil Steril 1994; 61: 219-235.
29. Elkins TE, Trenthem L. Potential for *in vitro* growth of common bacteria in solutions of 32% dextran 70 and 1.0% sodium carboxymethylcellulose. Fertil Steril 1985; 43: 497-481.
30. Sahin Y, Saglam A. Synergistic effects of carboxymethylcellulose and molecular weight heparine in reducing adhesion formation in the rat uterine horn model. Acta Obstet gynecol Scand 1994; 73: 70-73.
31. Elkins TE, Bury R, Ritter J, Ling F, Ahokas R, Homsey C,

Malinak LR. Adhesion prevention by solutions of sodium carboxymethylcellulose in the rat. I Fertil Steril 1984; 41: 926-928.
32. Bendich A, Machlin LJ. Safety of oral intake of vitamin E. Am J Clin Nutr 1988; 48: 612-619.
33. Hemadeh O, Chilukuri S, Bonet V, Hussein S, Chaudry IH. Prevention of peritoneal adhesions by administration of sodium carboxymethyl cellulose and oral vitamin E. Surgery 1993; 114: 907-910.
34. Sanfilippo JS, Booth RJ, Burns CD. Effect of vitamin E on adhesion formation. J Reprod Med 1995; 40: 278-282.
35. Brett AW, Garry RB. Vitamin E slows the rate of free radical-mediated lipid peroxidation in cells. Arch Bioche and Biophy 1996; 334: 261-267.
36. Irina B, David G, Thomas R. Effects of -Tocopherol on platelets and the coagulation system. Platelets 2001; 12: 389-394.
37. Pasquale P, Fabio MP, Luisa L. Vitamin E inhibits collagen-induced platelet activation by blunting hydrogen peroxide. Arterioscler Thromb Vasc Biol 1999; 19: 2542-2547.
38. Szuwart T, Brzoska T, Luger T. Vitamin E reduces platelet adhesions to human endothelial cells in vitro. Am J Hematol 2000; 65: 1-4.
39. Knighton DR, Hunt TK, Thakral KK, Goodson WH. Role of platelet and fibrin in the healing sequence. Ann Surg 1982; 196: 379-388.
40. Ellis H. The causes and prevention of intestinal adhesions. Br J Surg 1982; 69: 241-243.

개에서 Hyaluronic Acid와 Vitamin E의 병용이 복강수술 후 유착방지에 미치는 효과

배재성 · 장광호[1] · 권영삼 · 장환수 · 김정은 · 박세일 · 임재현 · 李文學 · 이승진
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요 약 : 개에서 hyaluronic acid(HA), vitamine E 및 두 약물의 병용이 복강수술 후 유착방지에 미치는 효과를 비교하고자 본 실험을 실시하였다. 실험견은 HA 처치군, Vitamin E 800 처치군, HA와 Vitamin E 800 처치군 그리고 HA와 Vitamin E 1600 처치군의 5개군으로 분류하고 각 군에 3두씩 배치하였다. 정중개복 후 회맹연접부를 확인하고 회장 쪽으로 5 cm 간격으로 5곳에 1×1 cm 크기로 찰과상을 유도하였다. HA는 0.1%로 하나의 찰과상 당 3 ml과 복강 내에는 체중 당 3 ml을 도포 하였다. Vitamin E는 수술 전 5일부터 수술 후 14일까지 800, 1600 IU의 용량으로 경구투여 하였다. 수술 3주 후에 유착발생빈도 및 정도를 평가하였다. 혈액학적 검사소견 상 WBC의 수치는 수술 1일 후 전군에서 최고치를 나타냈으나 4일 후부터는 감소하기 시작하여 14일에는 정상범위로 회복하였으며 전군에 있어서 유의적인 변화는 나타나지 않았다. Fibrinogen 수치는 수술 1일 후 전군에서 최고치를 나타냈으나 4일 후부터는 감소하기 시작하여 7일에 수술전 수치로 회복하였으며 전군에 있어서 유의적인 변화는 나타나지 않았다. 유착발생 장소는 장막-장간막(43.3%), 장막-장막(20%), 장막-대망막(5%), 장막-복막(1.7%) 순으로 발생하였다. 유착발생빈도는 HA와 Vitamin E 800 처치군 47%로 Vitamin E 800 처치군 100%, HA 처치군 80%, HA와 Vitamin E 1600 처치군 53%에 비해 낮았다. 유착형성은 HA 처치군, Vitamin E 800 처치군, HA와 Vitamin E 800 처치군 그리고 HA와 Vitamin E 1600 처치군에서 5.3±0.58, 7±1.00, 2.3±1.15과 3±1.00로 HA와 Vitamin E 800 처치군이 유의적인 감소를 보였다($p < 0.05$). 이상의 결과를 종합하면 복강수술 후 유착방지에 있어 HA와 800 IU Vitamin E 병용투여가 효과적이라고 사료된다.

주요어 : hyaluronic acid, vitamin E, 유착, 개복술, 개