

Study on prevention of adhesion formation by use of sodium carboxymethylcellulose and dextran 70

I. Adhesion formation by artificial injuries and its preventive effect of sodium carboxymethylcellulose and dextran 70 in rabbits

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Sodium carboxymethylcellulose 및 dextran 70을 이용한 유착형성 방지에 관한 연구

I. 토끼에서 인공창상에 의한 유착형성과 sodium carboxymethylcellulose 및 dextran 70의 유착방지 효과

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초 록 : 복강장기의 유착을 방지하기 위하여 토끼의 공장에 인공창상을 일으키고 sodium carboxymethylcellulose (SCMC)와 dextran 70을 단일 혹은 합제로 사용하여 이들의 유착방지 효능을 조사하였고, 아울러 체중의 변화를 조사함으로써 이들을 사용하였을 때 일어날 수 있는 부작용을 검토하였다.

인공창상에 의한 유착형성 유발빈도와 정도를 알아보기 위하여 토끼를 전신마취시킨 다음 개복수술을 시행하여 공장의 장막에 2cm 폭으로 3곳에 abrasion 또는 electrocautery를 실시하였던 바, 이러한 인공창상들이 유의성있는 높은 유착형성률(abrasion, 70%; electrocautery, 72.7%)과 심한 유착정도를 일으켰으며(abrasion, 1.80; electrocautery, 2.44), 체중의 감소를 가져왔다(abrasion, -2.5%; electrocautery, -9.9%). Abrasion보다는 electrocautery에 의한 자극이 더욱 심한 유착정도 및 체중감소를 보였으며 심할 경우 폐사를 일으키기도 하였다.

이러한 유착을 효과적으로 방지하기 위하여 1,2,3%의 SCMC 및 6,10%의 dextran 70 용액을 단일 또는 합제를 만들어 abrasion방법으로 공장에 인공창상을 일으킨 토끼의 복강내에 주입하고 수술 4주후에 복강을 열어 유착형성률을 조사하였다 바, 1% SCMC와 10% dextran 70의 합제(Synthetic soln)에서 가장 낮은 유착형성률(0%)을 보여 유착방지 효과가 가장 뚜렷하였다. 아울러 수술 4주일후 체중의 변화도 유의하게 일으키지 아니 하였다.

그러므로 유착방지제로서 synthetic solution을 사용하는 것이 가장 효과적이라고 사려된다.

Key words : adhesion, sodium carboxymethylcellulose, dextran, rabbit

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Introduction

Postoperative adhesion formation is one of the common complications following abdominal operations, biopsy, tuboplasty operations, surgical collection and transfer of oocytes and embryos in human and animals. It causes intestinal obstruction, indigestion, peritonitis, dysfunction of abdominal organs, infertility, abortion and even to death. Although numerous attempts were performed to prevent it by application of steroidal and non-steroidal anti-inflammatory agents,^{1,3,13,14,15} calcium channel blockers,¹⁸ fibrinolysis,^{9,10,19,20} antimetotics,⁸ and high molecular weight substances,^{2,5,6,7,9,16,17,20} their clinical efficacy was variable and unpredictable and sometimes these agents caused undesirable side effects of prolonged hemorrhage,^{3,4,10} loss of body weight,⁷ immunosuppression^{1,6,17} and increment of mortality.²⁰

In this study, the occurrence of postoperative intra-abdominal adhesion formation on jejunum in rabbits following abrasion or electrocautery was examined. A synergistic effect of sodium carboxymethylcellulose (SCMC) and dextran 70 solutions on the prevention of adhesion formation in the abdominal cavities of adhesion-induced rabbits was assessed by measuring the occurrence rates and grades of adhesion and the changes of body weight.

Materials and Methods

Animals: The animals used throughout this experiment were nonpregnant adult female New Zealand White rabbits. All were fed commercial rabbit chow and water *ad libitum*.

Adhesion induction: The rabbits were primed with gonadotropins of 100 IU of PMSG(SIGMA Chem. Co., USA) and 100 IU of hCG(SIGMA Chem. Co., USA) 72 hours apart. The animals were laparotomized at caudal midline under general anesthesia by the administration of xylazine HCl (Rompun, Pfizer Co., Korea) and ketamine HCl (Ketalar, Yuhan Pharm. Co. Korea).

The rabbits in the abrasion group(n=10) were abraded in 2 cm length at three sites on the serosa of

jejunum with a dry gauze until bleeding occurs, the rabbits in the electrocautery group(n=11) were cauterized in the same length and sites with an electrocauterizer, and the rabbits in the sham-operation group(n=10) were laparotomized only and no induction stimuli was applied.

Application of adhesion preventive solutions: The solutions of 1%(n=10), 2%(n=18) and 3%(n=11) SCMC(SIGMA Chem. Co., USA), 6%(n=8) and 10% (n=10) dextran 70(SIGMA Chem. Co., USA), and a synthetic solution of 1% SCMC and 10% dextran 70(n=12) were infused into the abdominal cavity of the adhesion induced rabbits by abrasion as described above on the jejunum at dose of 5 ml/kg of body weight, respectively. The rabbits in control group were infused with only 0.9% saline solution after the above abrasion treatment.

Evaluation of adhesion: The treated animals were reoperated 4 weeks later. The appearance and grades of adhesion in the operated sites were evaluated by Steinleitner(1988).

Calculation of body weight: The body weight of rabbits was calculated 4 weeks later and compared with the preoperated body weight.

Statistical analysis: The difference of adhesion grades and body weights between the groups was analyzed with T-test and the difference of incidence of postoperative adhesion formation between the groups was analyzed with Chi-square test.

Results

Adhesion induction by abrasion or electrocautery: Following adhesion induction on serosa of jejunum by abrasion and electrocautery, the rabbits were reopened 28 days later. The occurrence of postoperative adhesion formation and its grades were examined and summarized in Table 1. The artificial injuries of abrasion and electrocautery caused significantly($P<0.05$) high incidence of adhesion formation(70.0 & 72.7%), while two(20.0%) of the 10 sham-operated control rabbits showed adhesion formation. Two rabbits received electrocautery treatment were dead of severe adhesion of jejunum

accompanied with bloat in cecum, inflammation and necrosis on serosa of jejunum.

The mean grade of adhesion in abraded and electrocauterized rabbits was 1.80 and 2.44, respectively and significantly ($P < 0.001$) higher than that in sham-operated rabbits (0.40).

Changes in body weight following adhesion induction: Four weeks following adhesion induction by abrasion and electrocautery, the body weight of the rabbits were calculated.

As shown in Table 2, a loss of body weight was found in abraded rabbits (-2.5%) and electrocauterized rabbits (-9.9%), while the sham-operated rabbits showed 10.0% gain of body weight.

Prevention of adhesion with SCMC and dextran 70 solutions: Following adhesion induction by abrasion and infusion of the adhesion preventive solutions, the rabbits were reopened 28 days later. The occurrence of postoperative adhesion formation and its grade were examined and summarized in Table 3.

None of the 12 rabbits infused with the synthetic solution showed adhesion, while 7 of 10 rabbits in control group showed adhesion. Two of the 11 rabbits infused with 3% SCMC solution showed

adhesion and one of them died after infusion of the solution.

The mean grades of adhesion were highly significantly ($P < 0.001$) lower in the synthetic group (0.00) and 3% SCMC group (0.36) and significantly ($P < 0.05$) lower in the 2% SCMC group than the control group (1.80). The 1% SCMC, 6 and 10% dextran 70 solutions alone showed no significant adhesion reduction.

Changes in body weight following infusion of SCMC and dextran 70 solutions: Following adhesion induction by abrasion and infusion of the adhesion preventive solutions, the body weight of the rabbits was examined 28 days later. The changes of the body weight before and after infusion of the solutions were summarized in Table 4.

A slight increment of body weight was shown in the groups of 1% SCMC and 10% dextran 70, respectively. The rabbits infused with the synthetic solution showed -5.3% loss of body weight as well as the control group. 3% SCMC solution caused -6.6% loss of body weight. No significant difference in the change of body weight was seen following infusion of the solutions and among the treatment groups.

Table 1. Occurrence of postoperative adhesion formation and its grades in jejunum of rabbits following adhesion induction by abrasion or electrocautery

Treatment	No. of rabbits			Grade of adhesion					
	Used	Adhered(%)	Dead	0	+1	+2	+3	+4	Mean \pm SEM
Abrasion	10	7(70.0)*	0	3	0	3	4	0	1.80 \pm 0.42***
Electrocautery	11	8(72.7)*	2	2	0	3	4	1	2.44 \pm 0.42***
Sham-operation	10	2(20.0)	0	8	0	2	0	0	0.40 \pm 0.27

*.*** : denote the 5% and 0.1% statistical difference from sham-operation.

Table 2. Changes in body weight following adhesion induction by abrasion and electrocautery on jejunum in rabbits

Groups	No. of rabbits examined	Preoperation	Postoperation	Weight gain or loss
				(kg)
				(%)
Abrasion	7	3.41 \pm 0.26	3.33 \pm 0.13	-0.08(-2.5)*
Electrocautery	5	3.28 \pm 0.30	3.05 \pm 0.29	-0.17(-9.9)***
Sham-operation	7	3.14 \pm 0.18	3.46 \pm 0.14	+0.32(+10.0)

Each values are mean \pm SEM.

*.*** : denote the 5% and 0.1% statistical difference from sham-operation.

Table 3. Occurrence of postoperative adhesion formation and its grades in jejunum of rabbits following abrasion and infusion of SCMC and dextran 70 solutions.

Groups	No. of rabbits			Grade of adhesion					
	Treated	Adhered	Dead	0	+1	+2	+3	+4	Mean \pm SEM
1% SCMC	10	6(60.0)	0	4	2	2	2	0	1.20 \pm 0.39
2% SCMC	18	7(38.9)	0	11	0	5	1	1	0.94 \pm 0.31*
3% SCMC	11	2(18.2)*	1	9	0	2	0	0	0.36 \pm 0.24***
6% Dextran	8	6(75.0)	0	2	1	3	1	1	1.75 \pm 0.49
10% Dextran	10	6(60.0)	0	4	1	4	1	0	1.20 \pm 0.36
Synthetic	12	0(0.0)**	0	12	0	0	0	0	0.00 \pm 0.00***
Control	10	7(70.0)	0	3	0	3	4	0	1.80 \pm 0.42

***, **, * : denote the 5, 1 and 0.1% statistical difference from control.

Table 4. Changes in body weight in artificially adhesion induced rabbits infused with SCMC and dextran 70 solutions

Groups	No. of rabbits examined	Pre-operation	Post-operation	(kg)
				Weight gain or loss (%)
1% SCMC	7	3.49 \pm 0.09	3.56 \pm 0.10	+0.07(+2.0)
2% SCMC	18	3.42 \pm 0.08	3.29 \pm 0.09	-0.13(-3.8)
3% SCMC	9	3.49 \pm 0.13	3.26 \pm 0.09	-0.23(-6.6)
6% Dextran	8	3.41 \pm 0.20	3.31 \pm 0.11	-0.10(-2.9)
10% Dextran	10	3.35 \pm 0.12	3.42 \pm 0.10	+0.07(+2.1)
Synthetic	12	3.56 \pm 0.20	3.37 \pm 0.18	-0.19(-5.3)
Control	7	3.41 \pm 0.26	3.23 \pm 0.13	-0.18(-5.3)

Each values are mean \pm SEM.

No significant difference was shown within the column.

Discussion

Postoperative abdominal adhesions occur after an inflammatory response secondary to surgical trauma, ischemia, foreign bodies, hemorrhage and infection. Electrocautery and abrasion on serosal surface of jejunum caused high incidence and severe grade of adhesion formation and weight loss in rabbits. In rat experiments,²² electrocautery also caused severe adhesion in colon and uterine horns and caused to develop cecal bloat, dysfunction of GIT, peritonitis and to fatal death. These adhesions may result from trauma to tissue, accompanied by an inflammatory reaction, exudation of fibrinogen, fibroblastic proliferation, and organization of the fibrin matrix.

The pharmacologic basis for adhesion prophylaxis includes agents that decrease the inflammatory reaction, prevent blood coagulation and fibrin

deposition, inhibit fibroblastic proliferation, promote fibrinolysis, or mechanically separate the injured tissues. Several recent reports emphasize the intraperitoneal instillation of various high molecular weight solutions, particularly 3% SCMC, 25% chondroitin sulphate and 32% dextran 70.

SCMC is a water-soluble polymer derived from natural cellulose by reaction with monochloroacetate, and it is widely used in the food, cosmetic and pharmaceutical industries. Its molecular weight varies. Food grade forms exhibit a molecular weight of up to 350,000. Aqueous solutions of SCMC are clear, semigelatinous and highly viscous. The viscosity of 1% SCMC solution at 25°C is between 1,550-3,000 cps. Aqueous solutions of SCMC have been prepared that closely simulate the lubricating properties and viscosity of synovial fluid. In limited animal tests, SCMC injected into rabbit anterior eye chambers and

knee joints was nonirritating and caused no apparent damage.¹⁰ Dermatologic and toxicologic studies demonstrate that SCMC shows no evidence of being toxic to white rats, dogs, guinea pigs, or human beings. SCMC solutions appear to be absorbed more slowly from the abdomen than solutions of dextran.³ SCMC may also be less antigenic than dextran and less likely to support bacterial growth. Instillation of 10 ml of 10% dextran 70 into the abdomen of rats has resulted in death within 24 hours, an effect possibly mediated by an allergic response.⁶ Instillation of a similar volume of SCMC had no such effect. SCMC is highly effective in reducing postoperative adhesion in animals^{2,5,7,12,21,23} and possibly in human beings. The effect of SCMC in reducing adhesion formation was significantly dose-dependent. Fredericks et al⁷ found 12% loss of body weight in rabbits infused with 3% SCMC at dose of 7 ml/kg, but in this experiment an average weight loss of 6.6% was found in 3% SCMC treatment group because of low dose of 5 ml/kg.

Dextran 70 is a polysaccharide formed by the action of a bacterium, *Leuconostoc mesenteroids*, and has the average molecular weight of 70,000. It is widely used as a plasma expander. It has also been used as an adhesion preventive medicine because of its siliconizing property of coating raw surfaces, antithrombogenic property of fibrinolysis, and an osmotic agent prevent prolonged tissue apposition. The untoward reactions are mainly its antigenicity and immunosuppression by inhibiting the phagocytic activity of macrophage. Utian et al²⁰ reported that three of seven(43%) rabbits were dead after infusion of 30 to 50 ml of 32% dextran 70 in dextrose. Elkins et al⁶ reported that four(29%) of 14 rats died of peritonitis after receiving 32% dextran 70. In this experiment, by lowering the dose and concentration of dextran 70 solutions, no significant changes in body weight and in blood pictures including count of lymphocytes was found(unpublished data). The dextran solutions alone did not significantly reduced adhesion formation after injury, but when dextran 70 was used with SCMC, a synergistic effect of adhesion prevention was identified.

Numerous other materials can be considered, but use

of anticoagulants and fibrinolytics may be dangerous, steroids are controversial, and other anti-inflammatory agents, particularly antiprostaglandins, probably have a potential role but have not yet been fully tested on safety.

For the successful prevention of adhesions, the use of the synthetic solution with meticulous surgical technique and avoidance of infection may all be necessary.

A further study on the safety of this solution is under investigation.

Conclusion

In a preliminary study of adhesion formation following artificial injuries in jejunum, the abrasion and electrocautery caused significant adhesion formation(70 & 72.7%) and loss of body weight(-2.5 & -9.9%). None of the rabbits in the synthetic solution treated group showed adhesion formation, while 1% SCMC, 6 and 10% dextran solutions were also significantly effective in the prevention of adhesion formation. No significant($P < 0.05$) difference in the change of body weight was shown between the treated groups and control group.

Therefore, it can be suggested that the synthetic solution of 1% SCMC and 10% dextran 70 in 0.9% saline solution is prominently effective in the prevention of postoperative adhesion formation in rabbits and will be applicable to other animal and human beings.

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