Antiadhesive effect of the mixed solution of sodium hyaluronate and sodium carboxymethylcellulose after endoscopic sinus surgery

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ABSTRACT

Background: *We evaluated the clinical efficacy and safety of the mixed solution of sodium hyaluronate and sodium carboxymethylcellulose (HA-CMC) for prevention of adhesion after endoscopic sinus surgery.*

Methods: *Preoperative computed tomography (CT) scans were graded. At the completion of surgery, HA-CMC was applied to Merocel and repeatedly applied after the removal of Merocel. As a control, normal saline was applied. Endoscopic examination was performed postoperatively and grading was done.*

Results: *The rate of adhesion was the highest at 2 weeks postoperatively and was significantly lower in the HA-CMC–treated group than the control on all postoperative days. The grouping of cases by CT scores at 2 weeks postoperatively showed lower adhesion formation with the HA-CMC treatment than the control. The safety profile of the patients was normal at 4 weeks postoperatively.*

Conclusion: *HA-CMC is an efficacious and safe material in decreasing the incidence of adhesion after endoscopic sinus surgery.*

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Key words: Adhesion, endoscopic sinus surgery, postsurgical, revision surgery, sodium carboxymethylcellulose, sodium hyaluronate, surgical complication

Although the efficacy of endoscopic sinus surgery for the treatment of chronic sinusitis has well been established, the rate of revision surgery has been reported to range from 7.6 to 38%: The postsurgical adhesion is one of the major causes of the failed endoscopic sinus surgery.[1–4] To prevent such adhesion, spacer insertion, use of absorbable antiadhesive agents, topical steroid spray, partial middle turbinectomy, and medial transposition of middle turbinate have been used.[5–7] Among them, absorbable antiadhesive agents prevent the formation of adhesion by forming a physical barrier at the operation site.[8] For the materials of absorbable antiadhesive agents, oxidized regenerated cellulose, sodium hyaluronate (HA), sodium carboxymethylcellulose (CMC), and dextran have been used, and, recently, research on HA and CMC has been actively performed.[9–11]

HA is a ubiquitous high molecular weight substance normally contained in the synovial fluid, the vitreous humor, and the extracellular matrix. It is a glycosaminoglycan made of repeating disaccharide units of glucuronic acid and *N*-acetylglucosamine, which acts as a barrier substance and lowers the severity and intensity of adhesion resulting from the inhibition of fibrin formation by coating the exposed area and saturating the CD44 receptor of peritoneal mesothelium.[9,10,12] On the other hand, CMC is a relatively low molecular weight and water-soluble substance that is generated by the chemical modification of cellulose. Because the human body does not have enzymes to degrade it, it is not immediately absorbed and remains in the surface of tissue during mucosal healing, thus acting efficiently as a physical barrier.[13,14] HA has limitations as a physical barrier because it is degraded easily by hyaluronidase causing its half-life to be only 1–3 days.[11] As a means to overcome this limitation, it is used in combination with CMC, because CMC functions as a chemical bridge of HA and acts as a conglutinant as well as coating substance. Hence, the use of combination of these two is more effective than its single use.[15,16] The mixed form of HA and CMC (HA-CMC) have been suggested to be excellent in the prevention of adhesion in abdominal surgeries.[15,17,18] However, there are no clinical studies on the effect of HA-CMC for the prevention of adhesion after sinus surgery.

Nowadays, the film form of HA-CMC is commercially used in gynecologic and abdominal surgeries.[19,20] Even though the solution form of HA-CMC is not used frequently, it has its own advantages: It can easily spread over and widely coat the surface of tissue.[16] Thus, it can be effectively used after sinus surgery because the surface of the ethmoid cavity is easily coated with the solution form of HA-CMC. However, there have been no studies on the use of the solution form of HA-CMC. On the other hand, Merocel (Medtronic Xomed, Jacksonville, FL) is used to improve hemostasis and reduce adhesion formation after nasal surgery. Nevertheless, despite the use of Merocel, the rate of adhesion formation after sinus surgery is reported to be 8–18%.[8,21] According to the scintigraphic evaluation in rabbits, only 27% of CMC insufflated in nasal cavity was cleared in 3 hours postinsufflation.[22] Thus, CMC may be an excellent antiadhesive agent after sinus surgery because of its long residual time in the nasal cavity.

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However, if the solution of HA-CMC is applied to the ethmoid cavity, it may be washed away by gravity and mucociliary transport of nasal mucosa and diluted by mucus secretion and tissue transudation in the ethmoid cavity. If the solution form of HA-CMC is used to inflate Merocel and the inflated Merocel is kept in the ethmoid cavity, the antiadhesive effect of the solution form of HA-CMC can be investigated by comparing with Merocel packing inflated with only normal saline. Therefore, in this study, we examined the antiadhesive efficacy and safety of HA-CMC by applying it to inflate Merocel after endoscopic sinus surgery.

MATERIALS AND METHODS

Among chronic sinusitis patients determined to be eligible for surgery from January to June 2004, 24 adult patients who did not have a history of previous sinusitis surgery, allergy, asthma, aspirin intolerance, or systemic diseases were included in this study. The study protocol was approved by the institutional review board (subject 2003-146), and it was performed after obtaining the patient's informed consent. HA-CMC (a generous gift from Biorane, Seoul, South Korea) is a colorless and transparent solution, and HA and CMC were mixed as 0.25% (w/v) and 0.49% (w/v). The mixed solution was in a sterile condition, and the package of 6-mL solution contained in a 10-mL Luer lock syringe was used.

After performing preoperative paranasal sinus computed tomography (CT), the severity of sinusitis was graded as per Lund-MacKay scores.[23] In all patients groups, endoscopic sinus surgery was performed under general anesthesia by a single surgeon, and the assignment of the control group and the test group was randomized. The study was performed by a double-blind method in which the operator was different from the adhesion investigator. Ethmoidectomy (Eth) was performed on all patients, and the accompanying procedures were performed also on the other paranasal sinuses according to the lesions of each patient. In the test group, Merocel was inserted in the ethmoidectomized areas of the lateral nasal wall corresponding to the middle turbinate. Six milliliters of HA-CMC were subsequently applied to the Merocel and the packing was performed. Afterward, the Merocel was kept for 36–48 hours in an inflated condition. After the removal of Merocel, 6 mL of HA-CMC was applied again to the operation site, and the patients were discharged on the 3rd day after surgery. In the control group, Merocel was inflated with 6 mL of normal saline instead of HA-CMC. The Merocel was removed in a manner identical to the test group, and the patients were discharged after the application of normal saline. In both groups, during the 4 weeks after discharge, second-generation cephalosporin was prescribed and a topical steroid spray was used. On the first visit to the outpatient clinic, 1 week after surgery, the nasal cavity was examined using nasal endoscopes and the crust and blood clots in the nasal cavity and the ethmoid sinus were removed, and at least two to three times normal saline irrigation of the nasal cavity per day were prescribed.

The severity of adhesion after surgery was evaluated 1, 2, and 4 weeks after surgery by endoscopic examination, according to the method previously reported; it was classified as grade 0, (G0) no adhesions; G1, adhesions limited to the anterior tip of the middle turbinate; G2, adhesions in other portions of the middle turbinate and <10% of the middle meatus; and G3, adhesions >10% of the middle meatus.[24] The incidence rate of adhesion was evaluated 2 weeks after surgery according to the Lund-Mackay CT score and was considered to be relevant in only G0 patients without adhesion.

To evaluate the safety of HA-CMC before and 1 and 4 weeks after surgery, complete blood count, prothrombine time/partial prothrombine time (PT/PTT), routine chemistry test, urine analysis, electrocardiogram (EKG), and chest x ray were performed. All abnormal symptoms or signs and the change of clinical test results that developed during the experimental period were analyzed.

To analyze the difference of the Lund-Mackay CT scores and to investigate the incidence rate of adhesion according to such CT scores, ANOVA analysis was performed to examine the statistical significance between the two groups. Statistical significance was considered in cases with $p < 0.05$. In addition, the adhesion incidence rate noted during the observation period between these two groups was analyzed by Fisher's exact test, and the evaluation of safety was analyzed by χ^2-test. The cases with $p < 0.05$ were considered to be significant.

RESULTS

Study Population, CT Scores, and Surgery

The age of the subjects ranged from 18 to 61 years with an average of 40 years. There were 16 male subjects and 8 female subjects. Bilateral endoscopic sinus surgery was performed in two cases; therefore, the total number of cases for the control group was 22 and the test group included 22 cases. Between the control and the test groups, there was no significant difference in gender and age (male subjects, $p = 0.37$; female subjects, $p = 0.21$; age, $p = 0.12$) and, similarly, no difference in the preoperative CT score between the two groups was detected ($p = 0.39$; Table 1). As for surgery, in addition to Eth, middle meatal antrostomy (MMA), frontal sinusotomy (FS), and sphenoid sinusotomy (SS) also were simultaneously performed. In the control group, Eth + MMA were performed in 4 cases, Eth + MMA + FS was performed in 8 cases, and Eth + MMA + FS + SS was performed in 10 cases. On the other hand, in the test group, Eth + MMA was performed in 2 cases, Eth + MMA + FS was performed in 9 cases, and Eth + MMA + FS + SS was performed in 11 cases.

Postoperative Adhesion Incidence Rate and the Severity of Adhesion

The cases with adhesion severity higher than G1 were considered as the formation of adhesion. It was observed that

Table 1 **Demography of the subjects ($n = 44$)**

	Control	HA-CMC	p Value
Sex			
Male	14	16	0.37
Female	8	6	0.21
Age (yr)	33.7 ± 13.3	40.0 ± 14.8	0.12
CT scores*	7.5 ± 2.0	8.1 ± 2.8	0.39

**Lund-Mackay scores.*

the formation of adhesion in the control group on the 1st week after surgery was 23% (G1, 5%; G2, 16%; G3, 2%), 25% on the 2nd week (G1, 4%; G2, 18%; G3 3%), and 18% on the 4th week (G1, 8%; G2, 10%); thus, the highest adhesion rate was detected the 2nd week after surgery. In the test group, the cases with adhesion severity higher than G2 were not observed and the adhesion of G1 severity was formed in all cases and the adhesion incidence rate on the 1st week after surgery was 4%, was 9% on the 2nd week, and was 3% on the 4th week; the highest adhesion incidence rate was detected 2 weeks after surgery. Therefore, in both groups, the adhesion incidence rate was the highest 2 weeks after surgery (Fig. 1). Statistical analysis showed that, in all time points after surgery, the adhesion incidence rate was significantly lower in the HA-CMC–treated group ($p = 0.002$; Fig. 2).

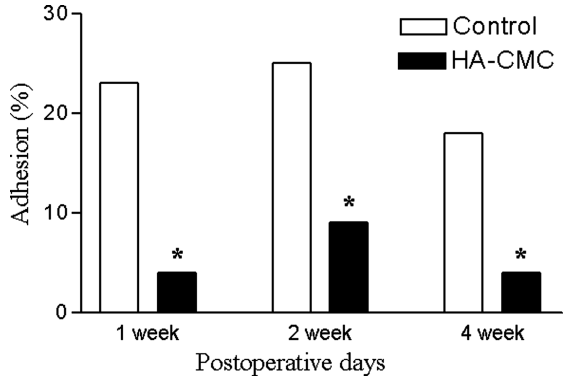

Figure 2. *Comparison of the adhesion incidence rate in the control and the HA-CMC–treated groups on each postoperative day. *$p < 0.05$ compared with the corresponding control group.*

Adhesion Incidence Rate 2 Weeks after Surgery According to the CT Score

The CT score was divided into groups of 4 points, and the adhesion incidence rate between the two groups was analyzed on the 2nd week after surgery. In the both groups, the number of patients with CT scores lower than 4 points was one case each. In the control group, the adhesion incidence rate in the cases with the CT score between 5 and 8 was 21% and in the cases with a score between 9 and 12 the score was 36%; thus, the adhesion incidence rate increased in the cases with higher CT scores ($p = 0.027$). In the test group, the adhesion incidence rate in the cases with the CT score between 5 and 8 was 6% and the adhesion incidence rate was 11% in the cases with a score between 9 and 12; the adhesion incidence rate showed a tendency to increase in the cases with a higher CT score. Nevertheless, a statistical difference was not observed ($p = 0.529$). In addition, in cases with CT scores between 5 and 8 and 9 and 12, the adhesion incidence rate in the test group was significantly lower than the control group ($p = 0.014$; Fig. 3).

Evaluation of Safety before and after HA-CMC Application

The laboratory tests performed before surgery and 1 and 4 weeks after surgery indicated no statistically significant difference between both groups ($p = 0.92$); in the test group on the 1st week, there was one case of leukocytosis accompanying upper respiratory tract infection and one case of temporary increase of SGOT (AST)/SGPT (ALT) after general anesthesia in a patient with fatty liver; however, the value was normalized 4 weeks after surgery in these two cases.

DISCUSSION

Most experts agree that routine nasal endoscopy with debridement is an important determinant of the success of endoscopic sinus surgery.[25,26] Despite these efforts, postoperative adhesion is troublesome to most clinicians. To study the availability of antiadhesive agents, it is the best way to use the agents without any other intervening materials. However,

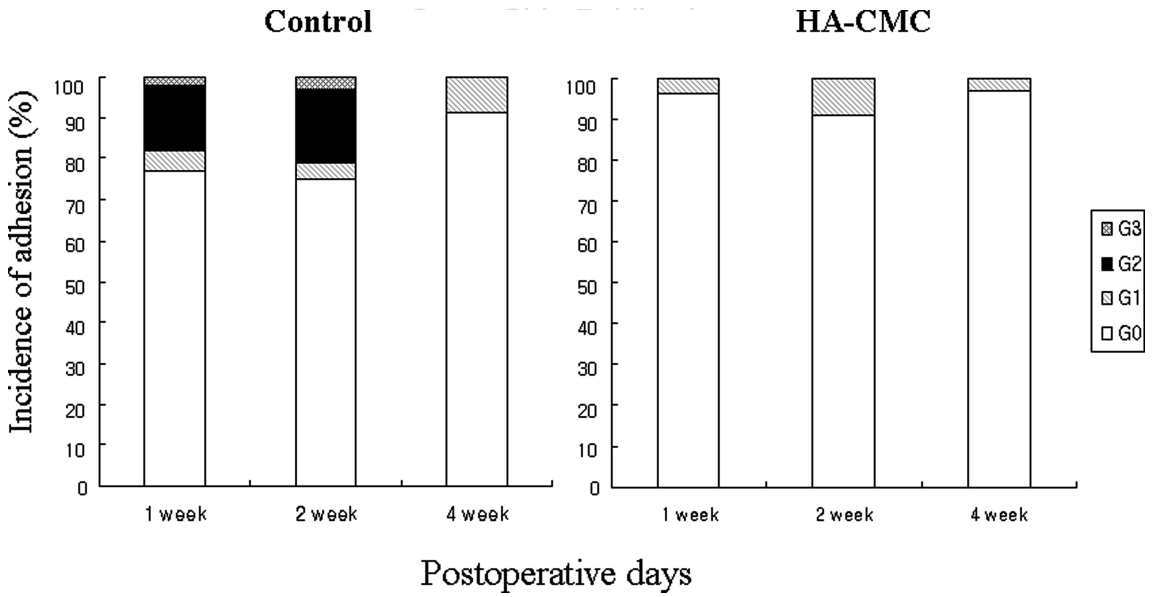

Figure 1. *Incidence and grading of adhesion in the control and the HA-CMC–treated groups on each postoperative day.*

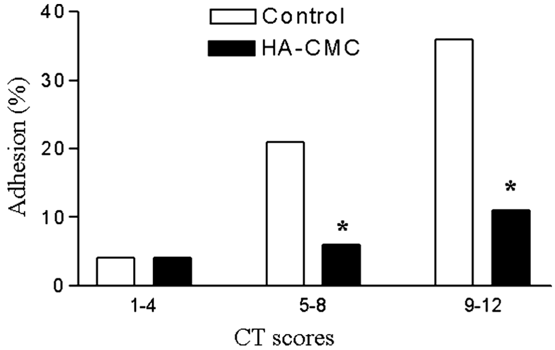

*Figure 3. Comparison of the adhesion incidence rate in the control and the HA-CMC–treated groups according to the CT scores at 2 weeks after surgery. *p < 0.05 compared with the corresponding control group.*

the antiadhesive agent used in this study is a solution type. Therefore, in this study, the control group had Merocel packing inflated with normal saline and the test group had Merocel packing inflated with HA-CMC.

In this study, the adhesion incidence rate was the highest at 2 weeks after surgery in both the control and the test groups, which is compatible with previous reports that the generation of adhesion and granulation tissue are most active 5–7 days after injury and adhesion becomes fixed approximately on the 14th day.[27] On the other hand, the result that adhesion being most abundant during the 2nd week was reduced during the 4th week is most likely because of the facts that the nasal cavity of patients was examined 1 week after surgery, that the crust and blood clots in the nasal cavity and the ethmoid area were removed, and that the irrigation of the nasal cavity with saline was started; because the mild adhesion could be resolved by such repeated treatment and irrigation, the formation of adhesion during the 4th week was less than the 2nd week.

In this study, the adhesion incidence rate during the interval after surgery was significantly lowered in the test group. Furthermore, G3 adhesion was detected in the control group, while adhesions higher than G2 were not detected in the test group, thus indicating milder adhesion in the test group. The results in this study are in good agreement with the report that HA and CMC suppress peritoneal adhesion in white rats and correlate well with the result of the study using Sepragel (Biorane), which is made of cross-linked HA,[9,15] implying that HA-CMC can be applied usefully in clinical fields. On the other hand, the formation of adhesions was increased in the cases with high Lund-Mackay CT scores, which is most likely because of the facts that the adjacent structures can be injured easily, the damage of the mucosa is increased in the cases with severe level of inflammation, and several areas have been operated.[4] According to the grouping based on CT score, the adhesion incidence rate in the HA-CMC–treated group was found significantly decreased in comparison with the control group; therefore, HA-CMC appears to suppress the formation of adhesion more effectively in the cases with more severe lesions.

Ideal antiadhesion materials should not only be effective in the prevention of adhesion, but also the agent itself or its degraded products should be safe, because it is inserted into the body.[14] HA is a ubiquitous substance normally contained in the body and can be regarded as a safe antiadhesive agent.[10] However, since CMC is generated by the chemical modification of cellulose and its degrading enzyme does not exist in the body,[13,14] its safety should be considered. According to an *in vivo* rabbit study, necrosis, squamous metaplasia, or ciliary degeneration was not observed 4 weeks after the insufflation of CMC particles.[28] Thus, CMC also could be considered as a safe substance. Furthermore, the fact that the application of HA-CMC to the peritoneum of white rats did not affect the growth of microorganisms supports its safety in endoscopic sinus surgery.[15] In this study, the homogeneity analysis of HA-CMC's safety as a medical substance shows no significant difference in the clinical laboratory tests before and after surgery.

The possible criticism on this study is that the antiadhesive effect of HA-CMC was only compared with the normal saline rather than comparing the separate effect of HA and CMC. Although HA and CMC can be used separately as an antiadhesive agent, if these agents are used simultaneously, the antiadhesive effect of the mixed solution would be more intense than that of each solution.[15,16] However, considering that these results were obtained from an animal model, human studies comparing the antiadhesive effect between the mixed solution and each solution should be performed in the future.

CONCLUSIONS

In this study, endoscopic sinus surgery by using HA-CMC was found to significantly prevent postoperative adhesion, and significant abnormal safety reactions were not detected. Therefore, it is thought that HA-CMC could be suggested for the use in a clinical field to reduce postoperative adhesion more effectively and safely.

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