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The Clinical Application and Efficacy of Sodium Hyaluronate–Carboxymethylcellulose During Tympanomastoid Surgery

Joong Ho Ahn, MD; Hyun Woo Lim, MD; Hye-Ran Hong, MD

Objectives/Hypothesis: To evaluate the anti-adhesive and anti-inflammatory effects of sodium hyaluronate–carboxymethylcellulose (HA-CMC) on postoperative hearing improvement and complications during tympanomastoid surgery.

Study Design: Prospective controlled clinical trial.

Methods: We evaluated 287 patients who underwent type I tympanoplasty, with or without canal wall up mastoidectomy, between January 2007 and June 2010. Postoperative hearing and complications were compared in the 143 patients who received Gelfoam soaked with HA-CMC during myringoplasty and the 144 patients who received Gelfoam only.

Results: There were no significant between-group differences in sex, age, and preoperative hearing status. However, average postoperative air-bone gap (13.7 ± 8.5 dB vs. 17.2 ± 9.9 dB) and the number of air-bone gaps smaller than 10 dB (40.6% vs. 24.3%) were significantly improved in the HA-CMC compared with the control group. In addition, the rates of reotorrhea, reperforation of the tympanic membrane (TM), postoperative TM adhesion, and reoperation were lower in the HA-CMC than in the control group without significances.

Conclusions: These findings suggest that combined application of Gelfoam with HA-CMC may be beneficial in patients undergoing tympanomastoid surgery.

Key Words: Hyaluronic acid, Gelfoam, packing, middle ear, tympanoplasty.

Level of Evidence: 2c.

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INTRODUCTION

Among the factors affecting the outcomes of tympanomastoid surgery are the surgeon's experience, tympanic membrane (TM) graft materials, eustachian tube function, and middle-ear packing agent.[1–4] Since otologic surgery was first used for the reconstruction of patients with chronic otitis media in 1952, various packing materials have been used to provide structural support for ossicular prostheses, tympanoplasty grafts, and external skin flaps.[5] Although absorbable gelatin sponge (Gelfoam; Medtronic Xomed Inc., Jacksonville, FL), consisting of purified porcine skin gelatins, is usually used for middle-ear reconstruction,[6] this material has been associated with adverse effects, including adhesion, fibrosis, osteoneogenesis, and ossicular fixation, resulting in suboptimal hearing outcomes in the middle ears of animals[7–10] and patients.[11]

Sodium hyaluronate (HA), a nonsulfated glycosaminoglycan polysaccharide, is inert, safe and easy to use and remains at biologic sites over extended periods of time.[7,12,13] Carboxymethyl cellulose (CMC), a cellulose derivative with carboxymethyl groups (-CH_2-COOH), has been used as a viscosity modifier or thickener, as well as to stabilize emulsions. Chemically modified sodium hyaluronate–carboxymethylcellulose (HA-CMC) is a bioresorbable agent shown to greatly reduce the incidence and degree of postoperative adhesions in patients, including those undergoing radical debulking procedures during abdominal and gynecologic surgery[14,15] as well as during thyroidectomy and mastoid surgery.[16,17] We have evaluated the anti-adhesive and anti-inflammatory effects of HA-CMC added to Gelfoam, when used for the reconstruction of TM during tympanomastoid surgery in patients with chronic otitis media, on postoperative hearing improvement and complications.

MATERIALS AND METHODS

Ethical Considerations

The institutional review board of the Asan Medical Center (Seoul, Korea) approved the study protocol, which conforms to the ethical standards of the Declaration of Helsinki published in 1964.

Patient Selection

This prospective, single-blinded study was performed in patients who underwent type I tympanoplasty (myringoplasty only), with or without canal wall up mastoidectomy (CWUM), from January 2007 to June 2010 in the Department of Otolaryngology of Asan Medical Center. We included patients who 1) had intact ossicular chains not eroded by inflammation or cholesteatoma; 2) showed patent eustachian tube orifices on

From the Department of Otolaryngology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

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Send correspondence to Joong Ho Ahn, MD, PhD, Department of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-2 dong Songpa-gu, Seoul 138-736, South Korea. E-mail: meniere@amc.seoul.kr

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TABLE I.
Demographic and Clinical Characteristics of the Sodium Hyaluronate–Carboxymethylcellulose and Control Groups.

	HA-CMC Group, n = 143	Control Group, n = 144	*P* Value
Gender, male:female, no.	63:80	72:72	NS
Age, yr, mean (SD)	50.2 (12.5)	50.2 (13.3)	NS
Side, right:left, no.	74:70	67:77	NS
Accompanied CWUM, no. (%)	117 (81.8)	120 (83.3)	NS
Average BC, dB HL (SD)	18.7 (9.6)	17.0 (11.2)	NS
Average AC, dB SL (SD)	40.4 (14.0)	39.9 (15.7)	NS
Air-bone gap, dB (SD)	21.7 (9.3)	22.9 (9.9)	NS
Air-bone gap <10dB, no. (%)	14 (9.8)	13 (9.0)	NS
Average follow-up, mo (SD)	16.9 (5.2)	16.7 (9.3)	NS

There were no significant between-group differences.
HA-CMC = sodium hyaluronate–carboxymethylcellulose; NS = not significant; SD = standard deviation; CWUM = canal wall up mastoidectomy; BC = bone conduction; AC = air conduction.

inspection during surgery; 3) had preoperative bone conduction at each frequency less than 65 dB HL, the limit of hearing measurements; and 4) were followed up for more than 1 year after initial surgery. We excluded patients who 1) had undergone previous tympanomastoid surgery on the same side and 2) showed the presence of an aditus block from severe granulation or cholesteatoma, which required posterior tympanotomy during mastoidectomy.

Patients were alternately assigned to receive HA-CMC and Gelfoam (n = 143) or Gelfoam alone (n = 144) during TM reconstruction.

Surgical Techniques for HA-CMC Application

All operations were performed by a single surgeon using standard techniques. In brief, the soft-tissue approach started with a 0.5-cm postauricular incision behind the posterior sulcus, followed by harvesting of the temporalis muscle fascia for reconstruction of the TM. CWUM was performed when preoperative temporal bone computed tomography scans showed decreased aerated mastoid air cells of soft-tissue density. At the end of the operation, the well-trimmed temporalis muscle fascia was inserted just beneath the inner surface of the perforated TM, with middle-ear packing materials interposed between the fascia and the middle-ear mucosal floor, especially on the promontory.

Gelfoam was thinly compressed, and small pieces (0.2 ~0.3 cm) suitable for packing were obtained. For patients in the HA-CMC group, the prepared Gelfoam pieces were soaked in HA-CMC solution (Guardix; Hanmi Medicare, Seoul, Korea), containing HA 2.5 mg and CMC 5 mg per 1 mL, before insertion into the middle ear. For patients in the control group, only Gelfoam pieces of the same size were inserted into the middle ear. Outer packing (rosebud packing) was performed using overlapping silk strips followed by pledgets of cotton soaked in antibiotic solution. The rosebud packing was left in place for 2 weeks to stent the reconstruction during preliminary healing and then gently removed with cotton wicks.

Follow-up and Audiologic Evaluation

All patients visited the outpatient department (OPD) twice weekly to have their dressing changed, until outer packing was completely removed around the third week. Patients again visited the OPD to assess the postoperative status of the wound and hearing after 1 month, and every 6 months thereafter.

Mean hearing levels in each patient were determined by averaging the hearing thresholds at 0.5, 1, 2, and 3 kHz, yielding the four-tone average (FTA). Pre- and postoperative air-bone gaps were measured, as were postoperative clinical outcomes, including the rates of re-otorrhea, reperforation of the TM, adhesive TM, and reoperation.

Statistics

All values are expressed as numbers or as means ± SDs, and significant differences between the HA-CMC and control groups were determined using Fisher exact test or the paired/unpaired t test, as appropriate, with statistical significance defined as $P < .05$. All statistical analyses were performed using Statistical Package for Social Sciences software (SPSS for Windows 12.0; SPSS Inc., Chicago, IL).

RESULTS

Preoperative Clinical Data

There were no significant differences between the HA-CMC and control group in sex ratio, mean age, side of operation, rate of accompanying CWUM, and mean follow-up (Table I). Preoperative bone and air FTA hearing thresholds were 18.7 ± 9.6 dB HL and 40.4 ± 14.0 dB HL, respectively, in the HA-CMC group and 17.0 ± 11.2 dB HL and 39.9 ± 15.7 dB HL, respectively, in the control group. There were also no significant differences between the HA-CMC and control groups in mean air-bone gap (21.7 ± 9.3 vs. 22.9 ± 9.9) or in the percentage of air-bone gaps smaller than 10 dB (9.8% vs. 9.0%).

Postoperative Clinical Data

Although there was no significant difference between the HA-CMC and control groups in postoperative bone conduction, postoperative mean air-bone gap was significantly higher (13.7 ± 8.5 dB vs. 17.2 ± 9.9 dB, $P < .05$) and the percentage of air-bone gaps smaller than 10 dB (40.6% vs. 24.3%, $P < .05$) was significantly higher in the HA-CMC than in the control group (Table II) (Fig. 1). There were no significant between-group differences, however, in the rates of re-otorrhea, reperforation of the TM, and adhesive TM, although the

TABLE II.
Postoperative Outcomes in the Sodium Hyaluronate–Carboxymethylcellulose and Control Groups.

	HA-CMC Group, n = 143	Control Group, n = 144	*P* Value
Average BC, dB HL (SD)	18.1 (10.2)	16.1 (10.6)	NS
Air-bone gap, dB (SD)	13.7 (8.5)	17.2 (9.9)	<.05
Air-bone gap <10 dB, no. (%)	58 (40.6)	35 (24.3)	<.05
Re-otorrhea, no. (%)	7 (5.0)	14 (9.9)	NS
Reperforation of TM, no. (%)	8 (5.8)	9 (6.3)	NS
Adhesive TM, no. (%)	3 (2.2)	8 (5.6)	NS
Reoperation, no. (%)	1 (0.7)	0 (0.0)	NS

HA-CMC = sodium hyaluronate–carboxymethylcellulose; BC = bone conduction; SD = standard deviation; NS = not significant; TM = tympanic membrane.

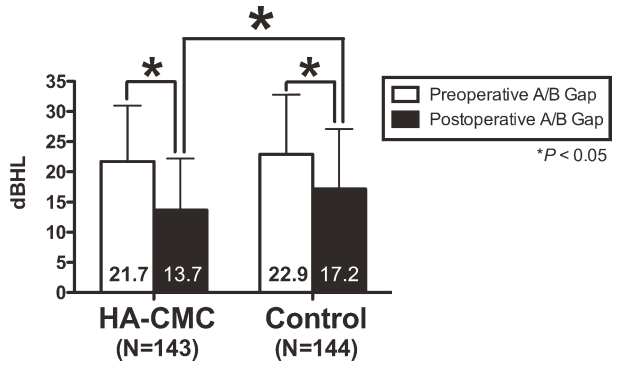

Fig. 1. Improvements in postoperative air-bone gap in the sodium hyaluronate–carboxymethylcellulose (HA-CMC) and control groups. Both groups showed significantly improvements in air-bone gaps ($P < .05$). Although the two groups showed no differences in preoperative air-bone gaps, postoperative air-bone gaps were significantly lower in the HA-CMC than in the control group ($P < .05$). A/B = air-bone.

HA-CMC group showed lower rates of postoperative complications than the control group.

Comparisons of Hearing Frequencies

When we analyzed pre- and postoperative air-bone gaps according to the hearing frequencies, we observed significantly improved postoperative air-bone gaps at each hearing frequency in both groups ($P < .05$) (Fig. 2). Postoperative air-bone gaps were significantly lower in the HA-CMC than in the control group at all hearing frequencies ($P < .05$), whereas the preoperative air-bone gap did not differ significantly between the two groups at any hearing frequency ($P > .05$).

DISCUSSION

Reconstruction of the ossicular chain and repair of TM perforations require supportive mechanisms within the middle-ear cavity. The ideal packing material for middle-ear reconstruction should be 1) sufficiently rigid to support the reconstructed TM, keeping it from drooping over the promontory; 2) biocompatible, allowing it to be absorbed after a sufficient period of time without leaving any foreign body that could induce recurrent infections; 3) nontoxic and nonallergenic, with minimum possibility of rejection; and 4) readily available.[6] Gelfoam, an absorbable gelatin sponge initially developed as an absorbable hemostatic device in neurosurgery,[18] has been used extensively in otologic surgery as supporting materials for TM and ossicular grafts, eustachian tube plugs, oval window sealant, and to repair skull base wound defects.[4]

Gelfoam has many favorable properties, including nonallergenicity, nontoxicity, biocompatibility, and most of all, ease of handling and designing.[9] It is an insoluble material that is eliminated within 2 to 9 weeks by proteolytic enzymes in adjacent tissue and by phagocytosis.[6] However, Gelfoam may be involved in the development of connective-tissue hyperplasia and inflammation, which may cause adhesion and fibrosis of the TM and ossicular grafts, leading to TM retraction and unfavorable hearing results.[9,10,19] Histologically, Gelfoam-treated middle ears of rats showed severe short-term acute inflammation with infiltration of fibroblasts and inflammatory cells, including polynuclear granulocytes and macrophages, and prominent long-term fibrosis.[7,9] In addition, Gelfoam may induce fibrosis by absorption of surrounding blood and fluid or by inducing the migration of fibroblasts through its porosity.[6,9,10]

Hyaluronate (HA) is an anionic, nonsulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues.[20] As one of the chief components of the extracellular matrix, HA contributes significantly to cell proliferation and migration and may also be involved in the progression of some malignant tumors. Inflammation after surgical trauma leads to the generation of many biologic factors, including growth factors, cytokines, and eicosanoids, which are necessary for subsequent wound healing by promoting the migration of inflammatory cells, fibroblasts, and endothelial cells into the wound site.[21] During the early inflammatory phases of wound repair, the wounded tissue contains high concentrations of HA, probably because of increased synthesis.[21] HA acts as a promoter of early inflammation, which is crucial for the entire wound healing process. HA may also function in the negative feedback loop of inflammatory activation through its specific interactions with the biologic constituents of inflammation.[21,22]

Since its efficacy in reducing connective-tissue formation was first shown in the middle ears of rats,[23] HA has been assessed as a possible substituent for Gelfoam in the treatment of perforated TM,[24] in sealing stapedotomy holes,[25] and in the promotion of postoperative re-epithelialization of the mastoid.[26] Owing to its ability to reduce postoperative fibrosis and adhesion in the middle ear,[23,27] HA should be considered a first-line material for middle-ear packing.

HA, however, may also decrease friction between the TM and graft, resulting in early migration of the

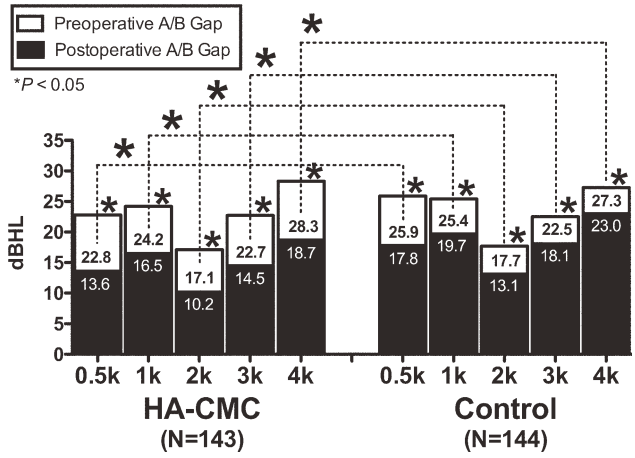

Fig. 2. Improvements in postoperative air-bone gaps according to hearing frequencies in the sodium hyaluronate–carboxymethylcellulose (HA-CMC) and control groups. Both groups showed significant improvements at each hearing frequency ($P < .05$). Although the two groups showed no differences in preoperative air-bone gaps, postoperative air-bone gaps were significantly lower at all hearing frequencies in the HA-CMC than in the control group ($P < .05$). A/B = air-bone.

graft before adequate healing.[28] Moreover, its clinical applications are limited by its light refractory capacity, low viscosity, rapid resorption, and short indwelling period in the middle-ear cavity.[28,29] Although chemically reprocessed HAs, such as MeroGel (Medtronics, Inc., Minneapolis, MN), Seprafilm (Genzyme Corp., Framingham, MA), and Sepragel (Genzyme Corp., Framingham, MA) were recently introduced, all have drawbacks, including the difficulty of trimming MeroGel into small pieces,[5] the 75~100-μm thickness of Seprafilm, making it difficult to fill the middle-ear cavity,[5] and the short duration of indwelling of Sepragel.[27]

We expected that the use of Gelfoam soaked in HA-CMC as a middle-ear packing material during tympanoplasty would decrease fibrosis while providing adequate support for the graft. Use of HA-CMC significantly improved postoperative hearing, including improved mean and frequency-specific air-bone gaps and an increased number of air-bone gaps smaller than 10 dB. Unlike HA, it is somewhat unclear whether CMC has ototoxic effects. A previous study reported CMC-induced hearing loss in guinea pigs without histologic proof[30]; others reported there were no hearing changes in both guinea pigs and humans when they applied HA-CMC in the middle ear and mastoid cavity.[17,31]

We suggest that the advantages of Gelfoam soaked in HA-CMC are its ease of use, including its ease of trimming; the lack of the need for additional time, compared with Gelfoam alone, for implantation; its effectiveness in preventing adhesion; its relatively longer residence within the middle-ear cavity; its lack of additional costs; and its synergistic benefits, such as improved hearing and decreased rates of postoperative complications. In addition, among the possible mechanisms by which Gelfoam soaked in HA-CMC improves hearing and reduces the rate of postoperative complications are the following: 1) its reduction of inflammatory tissue reactions and new bone formation, which may contract the space of the middle-ear cleft due to thickened mucosa; and 2) its decrease in fibrosis, which may trap the graft or newly forming TM in the adjacent structures such as the promontory. Filling of Gelfoam with HA was found to considerably reduce the formation of fibrous connective tissue and new bone in the rat middle ear, with intact TM neither retracted nor fixed to the underlying promontory.[23] Further studies are necessary to determine the methods to lengthen the time that HA remains in the mastoid cavity.

CONCLUSION

Gelfoam soaked in HA-CMC improved postoperative hearing and decreased complications compared with Gelfoam alone. These favorable results were likely due to reductions in inflammatory tissue reactions, new bone formation, and fibrosis, which may be induced by Gelfoam during middle-ear surgery. The use of Gelfoam soaked in HA-CMC may therefore be beneficial in patients undergoing middle-ear surgery.

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