CEO Clinical and Experimental Otorhinolaryngology Vol. 7, No. 1: 30-35, March 2014
http://dx.doi.org/10.3342/ceo.2014.7.1.30
pISSN 1976-8710 eISSN 2005-0720

Original Article

# A Randomized, Multi-Center, Single Blind, Active-Controlled, Matched Pairs Clinical Study to Evaluate Prevention of Adhesion Formation and Safety of HyFence in Patients After Endoscopic Sinus Surgery

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***Objectives.*** Recurrent mucosal disease and anatomic obstruction are commonly cited causes of failed endoscopic sinus surgery (ESS). Hyaluronic acid (HA) has been reported to reduce scarring and to promote wound healing in sinonasal surgery. HyFence is HA stabilized by 1, 4-butandiol diglycidyl ether, which makes it less-water-soluble and highly viscoelastic. The purpose of this study is to examine the anti-adhesion effect of HyFence after ESS compared to that of HA-CMC (Guardix-Sol).

***Methods.*** Seventy-four patients with chronic rhinosinusitis who underwent ESS were included in the study. After the ESS procedure, Merocel was placed in the ethmoidectomized areas of the both sides. Five milliliters of Guardix-Sol was then applied to the Merocel of one side and HyFence LV was applied to the other side. The effect of the agents was evaluated at one, two, and four weeks after surgery by endoscopic examination. The severity of adhesion, edema, infection and complications were evaluated.

***Results.*** There was no significant difference in the incidence of postoperative adhesion between the HyFence group and the Guardix-Sol group ($P>0.05$). Mean postoperative grades of edema and infection showed no significant difference between groups ($P>0.05$). There was no significant postoperative complications associated with either anti-adhesion agent ($P>0.05$).

***Conclusion.*** HyFence has equivalent anti-adhesion effect compared to Guardix-Sol following ESS.

***Keywords.*** *Endoscopic sinus surgery, Adhesion, Anti-adhesion agent, Hyaluronic acid, Complication*

## INTRODUCTION

Despite the established efficacy of endoscopic sinus surgery (ESS) for the treatment of chronic rhinosinusitis, recurrent symptoms that lead to revision surgery develop in 8%-38% of patients [1]. Recurrent mucosal disease and anatomic obstruction are commonly cited causes of failed ESS. In revision ESS, 56% of patients have adhesions, 27% have maxillary sinus ostium stenosis, and 25% have frontal sinus ostium stenosis [2]. In a review of 182 patients who underwent ESS, scarring of the maxillary antrostomy and ethmoid region was the only endoscopic finding that corresponded to poor symptom outcome [3]. Some authors advocate the use of mitomycin C intraoperatively to reduce fibrosis formation [4]. However, granulation tissue has been reported to form around the ostia following mitomycin C applica-

• Received November 15, 2012
Revised January 16, 2013
Accepted January 17, 2013

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tion [5].

Hyaluronic acid (HA) is a water-soluble ubiquitous polysaccharide component of the extracellular matrix. HA has been reported to reduce scarring and to promote wound healing in sinonasal surgery [6]. HA is used as an anti-adhesion agent in a mixed form with less absorbable material like sodium carboxymethylcellulose (CMC). Because the human body lacks enzymes to degrade CMC, HA and CMC mixture (HA-CMC) is not immediately absorbed and thought to remain on the surface of tissue during mucosal healing [7]. Previous studies have demonstrated the anti-adhesion efficacy and safety of HA-CMC after ESS [8]. HyFence is a gel type medical device that contains 2% HA stabilized by 1,4-butandiol diglycidyl ether. It is less water-soluble and highly viscoelastic sticky HA gel material,which remains in human body enough to block adhesion.

The purpose of this study is to examine the anti-adhesion effect of stabilized HA (HyFence) after ESS compared to that of HA-CMC (Guardix-Sol).

## MATERIALS AND METHODS

### Subjects

A randomized, multi-center, single-blinded, active-controlled, matched-pairs design study was performed at three University Hospitals in South Korea. Patients with chronic rhinosinusitis who were candidates for surgery from December 2010 to June 2012 were eligible for this study. Inclusion criteria included age greater than 19 years and less than 70 years and a diagnosis of bilateral chronic rhinosinusitis with the bilateral difference of Lund-Mackay computed tomography (CT) score less than 3. Exclusion criteria included unilateral chronic rhinosinusitis, a history of previous sinus surgery, massive polyposis, allergies, asthma, aspirin intolerance, and the presence of systemic diseases. The study protocol was approved by the Institutional Review Board (Korea University Guro Hospital, MD0814; Youido St. Mary's Hospital, The Catholic University Korea, SC09DDMT0057; Bundang CHA Hospital, BD2011-001M). Informed consent was obtained on all subjects prior to enrollment.

### Study medical agents

HA-CMC (Guardix-Sol) was obtained from Biorane (Seoul, Korea) and HyFence LV was obtained from CHA Bio & Diostech (Seoul, Korea) (Fig. 1). Both materials are applied with Merocel (Medtronic-Xomed, Jacksonville, FL, USA) after ESS. Complex viscosities of HyFence LV and Guardix-Sol used in this study were 320,264 centi-poise (cP) and 3,533cP, respectively.

### Protocol

In all patients groups, endoscopic sinus surgery was performed under general anesthesia by a single surgeon at each hospital. After mucosal infiltration of 2% lidocaine with epinephrine, uncinectomy and middle meatal antrostomy were performed without partial resection of middle turbinate. Standard endoscopic anterior and posterior ethmoidectomy was performed with forceps and debrider. The frontal recess was opened widely and the sphenoid sinus opening was widened inferomedially. After the ESS procedure, Merocel was placed in the ethmoidectomized areas of the both sides. Five milliliters of Guardix-Sol was then applied to the Merocel of one side and HyFence LV was applied to the other side. The site of application of the agents was chosen by random number assignments. After application, the Merocel was kept for 48 hours in an inflated condition. After removal of Merocel, 5 mL of each agent was applied again to the operative site and the patients were discharged home on the third day after surgery. During the four weeks following discharge, a second generation cephalosporin antibiotic was prescribed. On the first visit to the outpatient clinic, one week following surgery, the nasal cavity was examined using a nasal endoscope. Any encrusted tissue and blood clots in the nasal cavity and the ethmoid sinus were removed followed by the prescription for normal saline irrigation at least two to three times per day. The effectiveness of each agent was evaluated one, two, and four weeks after surgery by endoscopic examination.

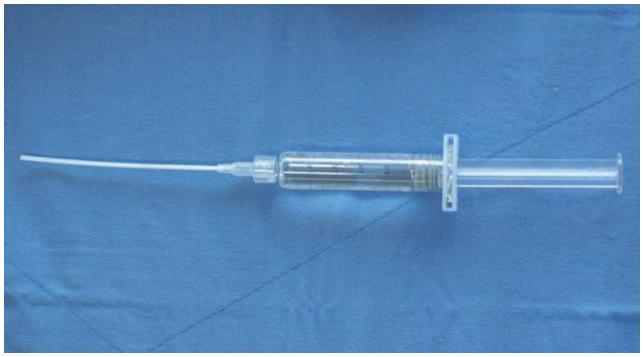

Fig. 1. HyFence LV contained in a syringe.

### Primary efficacy endpoint

At the four week follow-up visit, a blinded surgeon evaluated the presence of adhesions. The primary efficacy endpoint was defined as a difference between effectiveness of HyFence LV (Pt=P11+P10) and that of Guardix-Sol (Pc=P11+P01).

P11: The percentage of subjects with no adhesion on both sides.

P10: The percentage of subjects with adhesion on the Guardix-Sol side only.

P01: The percentage of subjects with adhesion on the HyFence LV side only.

### Secondary efficacy endpoint

The severity of adhesions was graded as follows: grade 0 (G0), no adhesions; G1, adhesions without limitation of sinus ventilation; G2, adhesions with limitation of sinus ventilation; and G3,

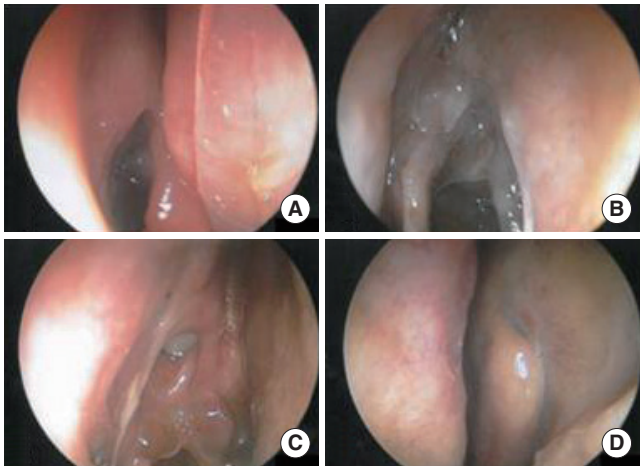


Fig. 2. Grading of the severity of adhesions. Group (G) 0 indicates no adhesion (A). G1 indicates adhesions without limitation of sinus ventilation (B). G2 indicates adhesions with limitation of sinus ventilation (C). G3 indicates total adhesion between the middle turbinate and lateral nasal wall (D).

total adhesion between middle turbinate and lateral nasal wall (Fig. 2). The severity of edema was graded as follows: grade 0 (G0) no edema; G1, mild edema without extinction of ethmoid cavity; G2, severe edema with extinction of ethmoid cavity; and G3, polyposis. The severity of infection was graded as follows: grade 0, (G0) no evidence of infection; G1, mild mucopurulent discharge; and G2, severe mucopurulent discharge. All grades were evaluated by a surgeon blinded to the application of the agents. To evaluate the safety of each agent, the vital signs, complete blood count, routine blood chemistry, urine analysis, an electrocardiogram, and a chest X-ray were obtained for each subject prior to the operation as well as at one, two and four weeks postoperatively. All abnormal symptoms or signs and abnormal laboratory or imaging results collected during the experimental period were analyzed.

### Statistical analysis

The statistical significance of the primary efficacy endpoint between the agents was analyzed using Wald test. The statistical significance of the secondary efficacy endpoint was analyzed using the McNemar test. A $P<0.05$ was accepted as statistically significant.

## RESULTS

A total 74 patients with bilateral chronic rhinosinusitis were enrolled in the study and two patients missed their visit in efficacy endpoints. The age of the subjects ranged from 20 to 67 years with a mean of 43 years. There were 57 male subjects and 15 female subjects. Severity of preoperative paranasal inflammation was comparable in both sides and there was no difference

Table 1. Preoperative Lund-Mackay PNS CT scores

| Paranasal sinuses | HyFence LV | Guardix-Sol | *P*-value |
|---|---|---|---|
| Maxillary sinus | 1.15±0.52 | 1.23±0.51 | 0.338 |
| Anterior ethmoid sinus | 1.27±0.51 | 1.26±0.50 | 0.870 |
| Posterior ethmoid sinus | 0.93±0.63 | 0.96±0.61 | 0.790 |
| Frontal sinus | 0.77±0.77 | 0.82±0.81 | 0.676 |
| Sphenoid sinus | 0.44±0.58 | 0.55±0.62 | 0.273 |
| Ostiomeatal complex | 1.40±0.92 | 1.37±0.94 | 0.859 |
| Total CT score | 5.96±2.04 | 6.19±2.15 | 0.503 |

PNS, paranasal sinus; CT, computed tomography.

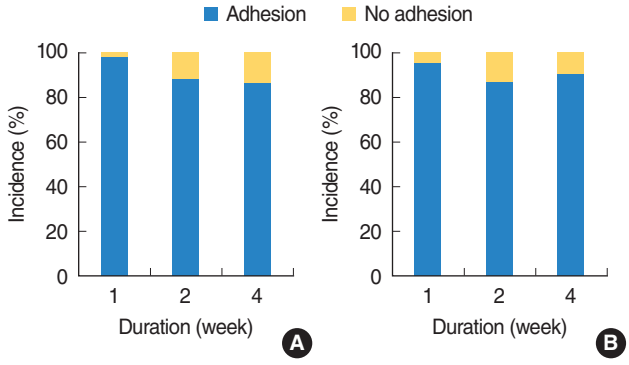


Fig. 3. Incidence of postoperative adhesions in HyFence LV (A) and Guardix-Sol (B).

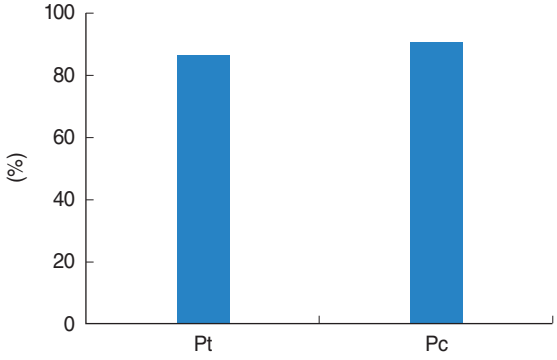


Fig. 4. The effectiveness of HyFence LV (Pt) and Guardix-Sol (Pc).

in the preoperative paranasal sinus computed tomography score between the two groups ($P>0.05$) (Table 1).

### Primary efficacy endpoint

The effectiveness of agents at one, two, and four weeks following surgery are shown in Fig. 3. Based on our definition of adhesion by agent applied, the calculated Pt was 0.861 and Pc was 0.903 (Fig. 4). The difference between effectiveness of HyFence LV and Guardix-Sol (Pd=Pt-Pc) was 0.042-0.102 which is the limit of the one-sided 97.5% confidence interval of Pd was higher than -0.12, the noninferiority limit. Based on our data, HyFence LV is not inferior to Guardix-Sol in terms of anti-adhesion effect.

Table 2. Postoperative number of cases that required treatment

| Week | HyFence LV | Guardix-Sol | | *P*-value |
|---|---|---|---|---|
| | | ≤G1 | ≥G2 | |
| 1st | ≤G1 | 71 | 0 | NA |
| | ≥G2 | 0 | 1 | |
| 2nd | ≤G1 | 71 | 1 | NA |
| | ≥G2 | 0 | 0 | |
| 4th | ≤G1 | 68 | 2 | 0.564 |
| | ≥G2 | 1 | 1 | |

Grade 0 (G0), no adhesions; G1, adhesions without limitation of sinus ventilation; G2, adhesions with limitation of sinus ventilation; G3, total adhesion between middle turbinate and lateral nasal wall.
NA, not applicable.

Table 3. Mean postoperative grades of adhesion

| Week | HyFence LV | Guardix-Sol | *P*-value |
|---|---|---|---|
| 1st | 0.49±0.74 | 0.42±0.65 | 0.526 |
| 2nd | 0.61±0.91 | 0.41±0.77 | 0.095 |
| 4th | 0.75±1.07 | 0.75±0.95 | 1.000 |

Values are presented as mean±SD.

## Secondary efficacy endpoint

### *Postoperative incidence of severe adhesions and the severity of adhesions by HyFence LV and Guardix-Sol*

Adhesions were evaluated at one, two, and four weeks after surgery by nasal endoscopic examination. Grades higher than G2 were considered to require treatment while grades less than G1 were considered to require no treatment. At week one, one case in each group had adhesions greater than G2. At week two, one case in the Guardix-Sol group had adhesions greater than G2. At week four, two cases in the HyFence LV group and three cases in the Guardix-Sol group had adhesions greater than G2 (Table 2).

Mean grades of postoperative adhesions are shown in Table 3. At the first, second and fourth weeks of follow-up, the mean grades were 0.49±0.74, 0.61±0.91, and 0.75±1.07 in the HyFence LV group and 0.42±0.65, 0.41±0.77, and 0.75±0.95 in the Guardix-Sol group. There was no significant difference between groups at each follow-up point ($P>0.05$).

### *Postoperative severity of edema in HyFence LV and Guardix-Sol*

Mean grades of the postoperative edema are shown in Table 4. At the first, second, and fourth weeks, mean grades of edema were 0.15±0.36, 0.15±0.36, and 0.13±0.33 in the HyFence LV group and 0.17±0.38, 0.14±0.35, and 0.13±0.33 in the Guardix-Sol group. There was no significant difference between groups at each follow-up point ($P>0.05$).

### *Postoperative severity of infection in HyFence LV and Guardix-Sol*

Mean grades of the postoperative infection are shown in Table 5. At week one, the mean grade was 0.04±0.20 in the HyFence LV group and 0.03±0.17 in the Guardix-Sol group. At week two, the mean grade was 0.03±0.17 in both groups. At week four, the mean grade was 0.01±0.12 in both groups. There was no significant difference between groups at each follow-up point ($P>0.05$).

Table 4. Mean postoperative grades of edema

| Week | HyFence LV | Guardix-Sol | *P*-value |
|---|---|---|---|
| 1st | 0.15±0.36 | 0.17±0.38 | 0.567 |
| 2nd | 0.15±0.36 | 0.14±0.35 | 0.567 |
| 4th | 0.13±0.33 | 0.13±0.33 | 1.000 |

Values are presented as mean±SD.

Table 5. Mean postoperative grades of infection

| Week | HyFence LV | Guardix-Sol | *P*-value |
|---|---|---|---|
| 1st | 0.04±0.20 | 0.03±0.17 | 0.321 |
| 2nd | 0.03±0.17 | 0.03±0.17 | 1.000 |
| 4th | 0.01±0.12 | 0.01±0.12 | 1.000 |

Values are presented as mean±SD.

### *Postoperative safety evaluation of HyFence LV and Guardix-Sol*

Laboratory results collected preoperatively and one, two, and four weeks after surgery indicated no statistically significant difference after surgery. There were two major postoperative adverse events with one patient diagnosed with a headache and the other with pneumonia. Both patients recovered following prolonged hospital admission. Both adverse events were considered to be unassociated with the anti-adhesion agents.

## DISCUSSION

After sinonasal surgery, regenerating epithelium and fibrous tissue may grow in damaged mucosal surfaces creating an adhesion. If the adhesion is extensive and locates near the ostium, it can lead to re-obstruction of the sinus ostium and result in recurrent sinus infections [4]. HA is a ubiquitous substance normally present in the human body and can act as an anti-adhesion agent by inhibition of fibrin formation when applied to exposed areas [9,10]. Previous studies have revealed that HA is an effective agent in preventing adhesion after sinus surgery [6,11,12]. HA has been used as an anti-adhesion packing agent not only in sinonasal surgery, but also in middle ear surgery and tympanic membrane repair surgery [13,14]. HA is also known to improve re-epithelialization after ESS [6,12]. Rapid wound healing by re-epithelialization minimizes the risk of adhesion and infection.

CMC is a relatively low-molecular-weight and water-soluble substance that is generated by modification of cellulose. Because humans lack enzymes to degrade CMC, it is not immediately absorbed and remains in the surface of tissue acting as a physi-

cal barrier. Thus, HA-CMC has been thought to be more effective in preventing adhesions. HA-CMC has demonstrated anti-adhesion effects in abdominal surgeries and sinonasal surgeries [8,15]. However, there have been no comparative study comparing the effect of stabilized HA and HA-CMC after ESS. Our study represents the first study to compare these two agents.

The results of our study suggest that there is no significant difference in the incidence of postoperative adhesion between the topical application of HyFence LV and Guardix-Sol. No difference was found in the mean adhesion grade at one, two, and four weeks of follow-up or in the number of cases requiring re-operation. In addition, mean postoperative grades of edema and infection showed no significant difference between groups.

It is known that the formation of adhesions and granulation tissue are most active within the fifth to seventh postoperative days suggesting that the effect of anti-adhesion agents is most important during this period [16]. According to Johns et al. [17], HA is easily degraded by hyaluronidase and its half-life is only one to three days. In this study, we applied HyFence LV and Guardix-Sol again after the removal of Merocel at 48 hours after the operation. Normally, HA would not have an effect until the seventh postoperative day. However, HyFence LV (HA stabilized by 1,4-butandiol diglycidyl ether) had enough viscoelasticity to remain at the operation site until postoperative day seven.

The effectiveness of the anti-adhesion agents in this study (86.1% in HyFence LV, 90.3% in Guardix-Sol) were somewhat lower than previous studies (more than 95% in MeroGel and Guardix-Sol) [6,8]. However, the majority of the adhesions observed were G1, which were non-obstructive by definition. Therefore, we consider these differences to be the result of the subjective nature of the evaluation. In addition, this study is a comparative study and these differences had no influence on the results of this study.

There were two major adverse events: a severe headache and pneumonia. Pneumonia was diagnosed before the surgery, so he was the one of the two patients who missed their visit in efficacy endpoints. Patient with headache recovered following a prolonged hospital admission and the complications were felt to be unassociated with the agents. Previous studies have revealed that the two agents, HA and CMC, are safe in sinonasal surgery [8,9,18]. Though CMC is generated by chemical modification of cellulose, it is as safe as HA in sinonasal application based on our results.

In summary, there was no difference in postoperative adhesions after application of HyFence and Guardix-Sol in sinonasal surgery. Therefore, HyFence has an equivalent anti-adhesion effect compared to Guardix-Sol after ESS and the two agents can be used safely after sinonasal surgery.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGMENTS

This study was supported by a grant of the Korea Healthcare Technology R&D Projects, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A090084) and CHA Bio & Diostech.

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