

# The evaluation of two new hyaluronan hydrogels as nasal dressing in the rabbit maxillary sinus

Qun Chen, M.D.,<sup>1</sup> Guangbin Sun, Ph.D., M.D.,<sup>1</sup> Yunyun Wang, B.A.,<sup>2</sup> Weiping Zhong, B.A.,<sup>2</sup> and Xiao Zheng Shu, Ph.D.<sup>2,3</sup>

## ABSTRACT

**Background:** The postoperative scarring, ostial stenosis, and adhesions after functional endoscopic sinus surgery for chronic rhinosinusitis remains a major problem. This study was designed to evaluate two new hyaluronan (HA) hydrogels for neo-ostium antistenosis and promoting wound healing in a rabbit maxillary sinus model.

**Methods:** The anterior wall of the maxillary sinus of 48 rabbits was removed to create a 4-mm circumferential wound both on the nasal and on the sinus sides. A rapid-gelling HA hydrogel or preformed HA hydrogel was filled randomly into the right or left sinus, while the opposite sinus served as blank control or was treated with Merogel (Medtronic Xomed Surgical Products, Jacksonville, FL) as control. The neo-ostium diameter and histological scores were evaluated and analyzed postoperatively.

**Results:** The neo-ostium diameter in the rapid-gelling HA hydrogel-treated side was significantly larger than that in the blank control side with a mean difference of  $1.46 \pm 0.99$  mm ( $p = 0.03$ ),  $1.30 \pm 0.61$  mm ( $p = 0.0087$ ), and  $1.60 \pm 0.25$  mm ( $p = 0.00015$ ) at 2, 3, and 4 weeks, respectively; the neo-ostium diameter in the preformed HA hydrogel-treated side at 2 weeks was significantly larger than that in the blank control side or Merogel control side with a mean difference of  $1.46 \pm 0.76$  mm ( $p = 0.002$ ) or  $0.54 \pm 0.36$  mm ( $p = 0.007$ ), respectively. The preformed HA hydrogel-treated side showed better histology scores at 2 weeks in heterophils, fibrosis, and osteogenesis than the blank control, and the chronic inflammation (lymphocyte/plasmacyte infiltration) was not prevalent.

**Conclusion:** During the postoperative follow-up period both of the two HA hydrogels significantly prevented neo-ostium stenosis and the preformed HA hydrogel promoted wound healing.

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Functional endoscopic sinus surgery is frequently performed for chronic rhinosinusitis refractory to medical management. Despite the advances in instrumentation and surgical technique, postoperative scarring, ostial stenosis, and adhesions between the middle turbinate and lateral nasal wall are the major complications, which may obstruct the normal mucociliary drainage pathway of the sinuses and even cause a recurrence problem.<sup>1–5</sup> Postoperative debridement has been routinely performed to manage scarring and adhesion formation but with limited success. Although nasal dressings have been widely used to try to prevent this complication, unfortunately, most of them have not been shown to have a significant impact both on the promotion of wound healing and on the prevention of ostial stenosis and adhesions, and may, in fact, elicit a foreign body inflammatory response and actually promote scarring.<sup>6–20</sup>

Hyaluronan (HA) is a nonsulfated glycosaminoglycan found in the extracellular matrix of all vertebrate tissues, which plays a multifunctional role in wound healing.<sup>21,22</sup> Recently, we had synthesized several *in situ* cross-linking HA hydrogels that showed excellent potential in wound healing and tissue regeneration.<sup>23–28</sup> These hydrogels prevented ostial stenosis and promoted wound healing in a rabbit maxillary sinus model. However, the major unsolved problem is the time-consuming preparation procedure and slow-gelling process, resulting in the difficulty in gel manipulation and retention in wounded sinuses.<sup>26,27</sup>

Therefore, a rapid-gelling HA hydrogel and a preformed HA hydrogel were developed. Here, these two hydrogels were evaluated as nasal dressing for preventing neo-ostium stenosis and promoting wound healing in a rabbit maxillary sinus model.

## METHODS

Q Chen and G Sun contributed equally to this work.

## Materials

The rapid-gelling HA hydrogel (Gel A) was prepared by a modified technology similar to the method that was described previously<sup>23,24</sup> but with a solution pH increased to 8.5 (rapid-gelling time, ~60 seconds).

The preformed HA hydrogel (Gel B; PureRegen Gel Sinus, BioRegen Biomedical, Changzhou, China) was a cross-linked hydrogel prefilled in a syringe developed by BioRegen Biomedical.

## Animal Model: Surgical Technique

A rabbit maxillary sinus model was used.<sup>26,27</sup> All animal procedures followed protocols approved by the Hospital Animal Care and Use Committee. Forty-eight male *Pasteurella*-free New Zealand white rabbits (3.5–4.0 kg) were sedated, and the anterior wall of the maxillary sinus was removed with a high-speed microsurgical drill. Wounds were created within the medial walls of the sinuses with a 4-mm cutting bur on the high-speed microsurgical drill, and epithelium was removed circumferentially on both the nasal and the sinus sides, resulting in a 4-mm through-and-through wound.

Before wounding, the rabbits were randomly assigned into four groups. In group I (16 rabbits), only one sinus side was randomly selected for the surgery and served as a blank control; in group II (16 rabbits), one side was randomly treated with Gel A and the opposite side served as a blank control; in group III (8 rabbits), one side was randomly treated with Gel B and the opposite side served as blank control; in group IV (8 rabbits), one side was randomly treated with Gel B and the opposite side was treated with Merogel (Medtronic

From <sup>1</sup>Department of Otolaryngology, Shanghai Pudong New Area Gongli Hospital, Shanghai, China, <sup>2</sup>Research and Development Department, BioRegen Biomedical (Changzhou) Co., Ltd., Changzhou, China, and <sup>3</sup>School of Pharmaceutical Engineering and Life Science, Changzhou University, Changzhou, Jiangsu, China

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Address correspondence and reprint requests to Xiao Zheng Shu, Ph.D., BioRegen Biomedical (Changzhou) Co., Ltd., 167-5 East East Road, Changzhou 213025, China  
E-mail address: xzshu@bioregenmed.com

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Xomed Surgical Products, Jacksonville, FL) as control. The periosteum and skin incision were closed with a running suture.

### Ostium Size

At postoperative week 2, 6–8 rabbits in each group were killed with i.v. Beuthenasia (Schering-Plough Animal Health Corp., Union, NJ). Immediately after death, the healed wounds were opened and the sinuses were exposed. Next, the medial walls of the sinuses were examined using a 30° nasal telescope (FuAO, Tonglu, China) with video recording. An observer blinded to the treatment observed the videotape under magnification and determined the diameter of each neo-ostium using digital caliper.<sup>27</sup>

At postoperative week 3, a second surgery was performed in 16 rabbits (8 each in groups I and II) under anesthesia to determine the neo-ostium diameter as described previously. Next, the periosteum and skin incision were closed with a running suture and housed for another week. At week 4 after initial surgery, these rabbits were killed and the neo-ostium diameter was determined as described previously.

### Histological Analysis

After neo-ostium diameter determination at 2 weeks, the medial wall of each maxillary sinus was gently harvested, decalcified, and stained. A blinded pathologist evaluated histological sections of the healed surgical neo-ostium. Slides were examined using light microscopy and scored on a 5-point scale, with 0 being absent and 4 being severe. Each specimen was evaluated for the amount of heterophils, macrophages, fibrosis, lymphocytes/plasmacytes, epithelial growth, and osteogenesis.<sup>26,27</sup>

### Statistical Analyses

All statistical analyses were performed using a Student's *t*-test; a value of  $p < 0.05$  was considered significant.

## RESULTS

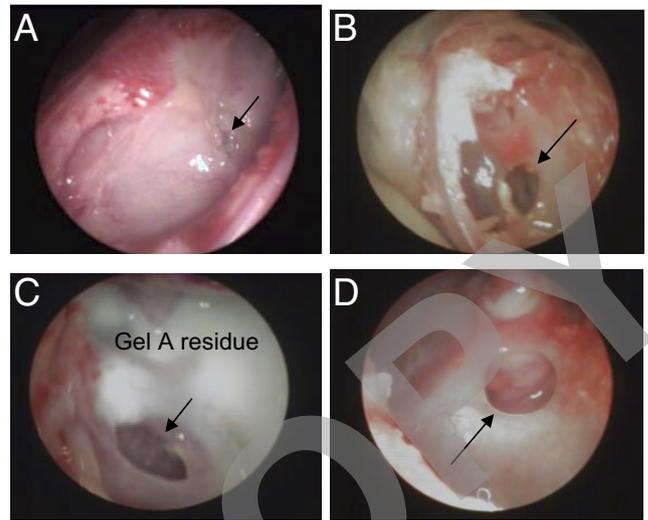
Forty-four of 48 rabbits completed the study. Three rabbits (two in group I at the initial surgery and one in group II at second surgery) died because of an anesthetic accident, and one rabbit in group IV at the initial surgery was killed after a handling accident. At 2 weeks, 29 rabbits (6 in group I, 8 each in groups II and III, and 7 in group IV) were killed for the neo-ostium diameter measurement and histological analysis. At 3 weeks, the remaining 16 rabbits in groups I (8) and II (8) were performed with a second surgery under anesthesia to measure the neo-ostium diameter, and the surviving 15 rabbits were housed for another week and then killed for the neo-ostium diameter measurement.

### Ostium Size

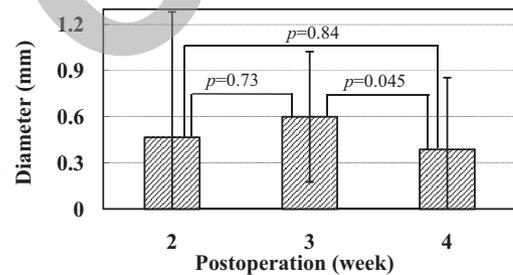
The overview of blank control and Gels A- and B-treated sinuses at 2 weeks was shown in Fig. 1. In general, the blank control neo-ostium in group I was almost completely closed (Fig. 1 *a*) and, surprisingly, that in group II with the opposite side treated with Gel A preserved some opening (Fig. 1 *b*). The Gels A- and B-treated neo-ostium preserved a wide opening (Fig. 1, *c* and *d*).

A lot of Gel A residue was found at 2 weeks (Fig. 1 *c*) and even at 4 weeks some residue still could be seen. The Gel B elimination was much faster and only a small amount of residue could be found in some sinuses at 2 weeks (Fig. 1 *d*).

With an initial diameter of 4 mm, the neo-ostium opening was further evaluated by measuring its postoperative diameter with a larger value showing better opening preservation. In the blank control group I, the mean diameters at 2, 3, and 4 weeks were  $0.47 \pm 0.82$  mm,  $0.6 \pm 0.42$  mm, and  $0.39 \pm 0.47$  mm, respectively, with a significant decrease from 3 to 4 weeks ( $p = 0.045$ ; Fig. 2). In group II, the mean diameters at 2, 3, and 4 weeks in the blank control side were



**Figure 1.** The overview of neo-ostium at 2 weeks (a) the blank control side in group I, (b) the blank control side in group II, (c) the Gel A-treated side in group II, and (d) the Gel B-treated side in group III.



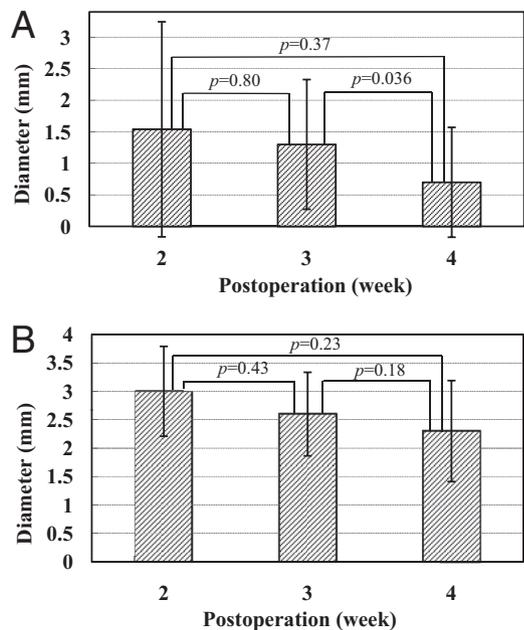
**Figure 2.** The mean neo-ostium diameters in group I (blank control) at 2 weeks ( $n = 6$ ), 3 weeks ( $n = 8$ ), and 4 weeks ( $n = 8$ ).

$1.54 \pm 1.71$  mm,  $1.30 \pm 1.03$  mm, and  $0.70 \pm 0.87$  mm, respectively, with a significant decrease from 3 to 4 weeks ( $p = 0.036$ ; Fig. 3 *a*), and the value at 2, 3, and 4 weeks in Gel A-treated sides were  $3.00 \pm 0.79$  mm,  $2.60 \pm 0.73$  mm, and  $2.30 \pm 0.89$  mm, respectively, but with an insignificant decrease from 3 to 4 weeks ( $p = 0.18$ ; Fig. 3 *b*). These results indicated that the second surgery at 3 weeks simulating the postoperative debridement in human sinus surgery did cause additional neo-ostium stenosis, especially without Gel A treatment.

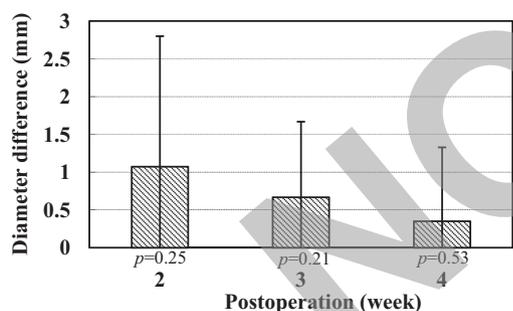
The mean diameter differences between the blank control side in groups I and II were calculated from the data in Figs. 2 and 3 *a*, and the value at 2, 3, and 4 weeks were  $1.07 \pm 1.73$  mm ( $p = 0.25$ ),  $0.67 \pm 1.00$  mm ( $p = 0.21$ ), and  $0.35 \pm 0.98$  mm ( $p = 0.53$ ), respectively (Fig. 4).

The mean diameter differences between the control and treated side were also calculated with a larger value showing better opening preservation. Using the data of the blank control side in group II (Fig. 3 *a*) and also the data of blank control group I (Fig. 2), the mean diameter differences of Gel A treatment were calculated and shown in Fig. 5, *a* and *b*, respectively. In Fig. 5 *a*, the mean diameter differences at 2, 3, and 4 weeks were all significant with the values of  $1.46 \pm 0.99$  mm ( $p = 0.03$ ),  $1.30 \pm 0.61$  mm ( $p = 0.0087$ ), and  $1.60 \pm 0.25$  mm ( $p = 0.00015$ ), respectively. In Fig. 5 *b* the mean diameter differences at 2, 3, and 4 weeks were also all significant with the values of  $2.53 \pm 1.04$  mm ( $p = 0.00061$ ),  $1.97 \pm 0.76$  mm ( $p = 0.0017$ ), and  $2.04 \pm 0.89$  mm ( $p = 0.0056$ ), respectively.

Gel B treatment also significantly improved the neo-ostium opening at 2 weeks. In group III the mean diameters in the Gel B-treated



**Figure 3.** The mean neo-ostium diameters in group II at 2 weeks ( $n = 8$ ), 3 weeks ( $n = 7$ ), and 4 weeks ( $n = 7$ ): (a) the blank control side, (b) the Gel A-treated side.



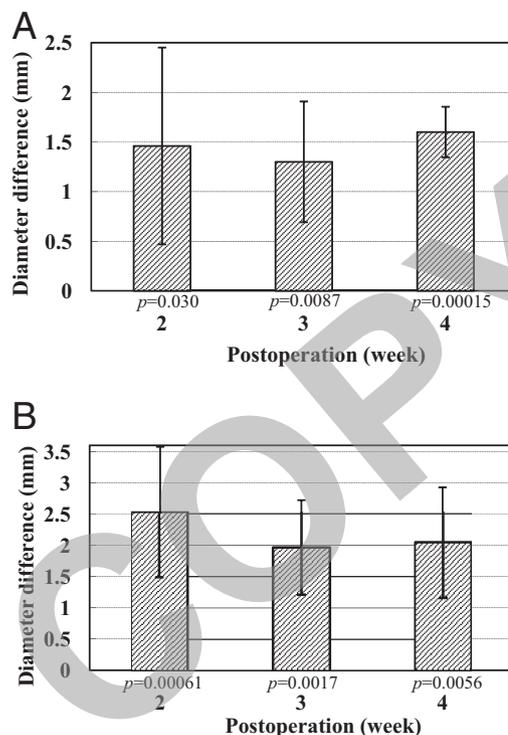
**Figure 4.** The mean neo-ostium diameter difference between the blank control side in groups II and I.

and blank control side were  $2.21 \pm 0.39$  mm and  $0.75 \pm 0.70$  mm, respectively, with a mean difference of  $1.46 \pm 0.76$  mm ( $p = 0.002$ ). In group IV, the mean diameters in Gel B-treated and Merogel control sides were  $2.07 \pm 0.28$  mm and  $1.53 \pm 0.47$  mm, respectively, with a mean difference of  $0.54 \pm 0.36$  mm ( $p = 0.007$ ) (Table 1).

### Histological Analysis

The histological analysis at 2 weeks was performed, and a paired analysis of the histological scores was performed to minimize variability among the subjects.<sup>26,27</sup> The score for each control side (blank or Merogel control) was subtracted from the treated side and the difference was recorded (Table 2). A greater difference between the two sides indicated a greater degree of inflammation, epithelialization, or osteogenesis associated with the gels.

As expected, that the chronic inflammation was not as prevalent at the 2 weeks<sup>27</sup> and the degree of lymphocyte/plasmacyte infiltration was similar in all three groups ( $p > 0.5$ ). In group III when compared with blank control, Gel B treatment had similar macrophage infiltration and insignificantly improved epithelialization ( $p = 0.35$ ), but significantly reduced the more acute inflammation including heterophile infiltration ( $p = 0.033$ ), fibrosis ( $p = 0.0001$ ), and osteogenesis



**Figure 5.** The mean neo-ostium diameter difference at 2, 3, and 4 weeks: (a) Gel A-treated side in group II minus the blank control side in group II; (b) Gel A-treated side in group II minus the blank control side in group I.

( $p = 0.011$ ); in group IV, when compared with Merogel control, Gel B treatment significantly reduced fibrosis ( $p = 0.017$ ), but the reduction of heterophils ( $p = 0.078$ ), macrophages infiltration ( $p = 0.17$ ), and osteogenesis ( $p = 0.17$ ) and also the improvement of epithelialization ( $p = 0.36$ ) were not significant. In group II, when compared with the blank control, Gel A treatment significantly reduced fibrosis ( $p = 0.033$ ) and osteogenesis ( $p = 0.033$ ) but with slightly higher heterophile and macrophage infiltration ( $p > 0.5$ ).

### DISCUSSION

Limited progress was achieved for nasal dressings to quickly restore normal sinus function by enhancing wound healing and minimizing the formation of scar tissue and adhesion after functional endoscopic sinus surgery.<sup>1-20</sup> In our opinion, three major factors should be carefully considered in designing better nasal dressing. The first is the material safety including its degraded fragments, the second is the material capability in promoting scar-free wound healing, and the third is the cross-linking/modification technology that should be carefully selected and precisely controlled to give a suitable retention and absorption time of materials in wounded sinuses without hurting biocompatibility and capability in improving scar-free wound healing.

HA is believed to be well suited to nasal dressing application. Both fermented HA and animal source HA have identical structures with well biocompatibility as that in the extracellular matrix of all vertebrate tissues and play a multifunctional role in wound healing.<sup>21,22</sup> HA scavenges reactive oxygen species and promotes keratinocyte proliferation and migration<sup>29</sup> and enhances wound reepithelialization.<sup>22</sup> Degraded HA fragments modulate the inflammatory response and stimulate angiogenesis.<sup>30</sup> The prolonged presence of HA in fetal and young animal's wounds are believed to be the major cause of the markedly reduced fibrous scarring.<sup>21</sup>

Table 1 Neo-ostium diameter (mm) in group IV at 2 wk

Rabbit No.	1	2	3	4	5	6	7	Mean ± SD
Gel B-treated side	1.8	2.2	2.4	2.1	2.1	1.6	2.3	2.07 ± 0.28
Merogel control side	1.5	1.8	2.0	1.8	1.8	0.7	1.1	1.53 ± 0.47
Diameter difference*	0.3	0.4	0.4	0.3	0.3	0.9	1.2	0.54 ± 0.36

\* $p = 0.007$ .

Table 2 Histology scores

Group	II	III	IV
Heterophils	0.1	-0.5	-0.4
Macrophages	0.1	0	-0.3
Fibrosis	-0.5	-1.3	-0.9
Lymphocytes/plasmocytes	0.0	0.0	0.0
Epithelials growth	0.0	0.1	0.1
Osteogenesis	-0.5	-0.6	-0.3

Scores are means of differences between treatment and control values. Positive numbers indicate a greater presence of the finding in treated sides.

The major limitations of HA are its fluid nature and rapid degradation, leading to a too short residence time in the wounded sinuses. Therefore, cross-linking/modification should be applied. However, until now the effort to develop HA nasal dressing shows limited success possibly because of the excessive and inappropriate cross-linking/modification,<sup>11-19</sup> which might worsen the biocompatibility and compromise its unique capability in scar-free wound healing and thus result in inflammation or negligible efficacy, such as in the case of the highly benzyl esterification of HA (Merogel)<sup>11-17</sup> and the ferric cross-linked HA (Intergel, Lifecore Biomedical, Chaska, MN) that was withdrawn from the market because of possible Intergel reaction syndrome (pIRS).<sup>31</sup>

The two new HA hydrogels evaluated in this study are both cross-linked through our novel thiolated chemistry and the modification/cross-linking had been precisely designed and controlled. Gel A is an *in situ* gelling hydrogel formed right before filling by mixing two components, and the mixture solution becomes viscous and rapidly lost its fluidity to form a solid gel in the wounded sinus within ~60 seconds, which is more than six times faster than the slow-gelling process in a previous report.<sup>27</sup> This rapid gelling is desirable in a clinical setting and is important for the material retention in the wounded sinuses, especially the ethmoid cavity. On the other hand, Gel B is a preformed hydrogel with high viscoelasticity and prefilled in the syringe, which is easy to use simply by injecting into the wounded sinuses.

The *in situ* rapid-gelling Gel A filled as a whole uniform gel with very high dynamic viscosity (>100,000 mPa · s) and suited the complicated 3D architecture of the wounded sinus well, and the retention and absorption was >4 weeks. The retention and absorption of Gel B in the wounded sinus was also prolonged (~2 weeks) because of its high dynamic viscosity (near 100,000 mPa · s) that is ~10 times higher than the dynamic viscosity of original HA and also much higher than the dynamic viscosity of those HA gels composed of dispersed cross-linked particles. The long and continuous presence of Gels A and B and also their gradually degraded HA fragments may improve the wound healing, minimize the formation of scar tissue, and preserve neo-ostium opening. In general, unlike Sepragel (dispersed HA particles)<sup>19</sup> refills of Gels A or B might not be necessary during the treatment.

Both Gel A and Gel B significantly improved the neo-ostium opening. At 2, 3, and 4 weeks the mean diameter in the Gel A-treated side was ~100~300% higher than that in the blank control side in the same rabbit (Fig. 3, a and b) and ~300~500% higher than that in the blank control

side of group I (Figs. 2 and Fig. 3 b). Moreover, in the same animal model, the mean diameter at 2 weeks of Gel A treatment increased ~30% when compared with the best slow-gelling hydrogel in previous reports (3.00 ± 0.79 mm versus 2.38 ± 0.30 mm).<sup>27</sup> As for Gel B treatment, the mean diameter at 2 weeks was ~200% higher than that in the blank control side and ~35% higher than that in the Merogel control side in the same rabbit (Table 1) and >300% higher than in the blank control side of group I at 2 weeks (Fig. 2).

Gel B treatment showed better histological scores in the more acute inflammation (heterophile infiltration, fibrosis osteogenesis, and macrophage infiltration) and also epithelialization than the blank and Merogel control and also Gel A treatment (Table 2). As for Gel A, the biocompatibility and promotion in wound healing had been justified by many HA hydrogels with very similar compositions.<sup>23-28</sup> Compared with Gel A, less HA original structure in Gel B was cross-linked and thus it was anticipated that it would be more capable of scar-free wound healing and better biocompatibility, which was confirmed by the histological results in this study (Table 2). In a separate study the biocompatibility of Gels A and B had been extensively investigated according to ISO 10993 standards (biological evaluation of medical devices), and the results showed that the biocompatibility of Gel B was comparable with the original HA and better than Gel A (XZ Shu, 2011 unpublished result).

Based on the encouraging results in this study, the preformed HA hydrogel (Gel B) has been selected for an impending multicenter, randomized, parallel group and controlled trial in human sinus surgery and the preliminary result confirmed its safety and significant treatment outcomes in wound healing, minimizing the formation of scar tissue, which will be reported soon.

## CONCLUSIONS

In this study during the postoperative follow-up period both of the two new HA hydrogels significantly prevented the neo-ostium stenosis and the preformed HA hydrogel promoted wound-healing.

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