The clinical outcomes of new hyaluronan nasal dressing: A prospective, randomized, controlled study

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ABSTRACT

Background: *Poor postoperative wound healing after endoscopic sinus surgery (ESS) remains a significant problem. This study evaluates the efficacy and safety of a new absorbable hyaluronan hydrogel.*

Methods: *A prospective, randomized, controlled trial was conducted. Fifty-five patients with bilateral ESS were recruited and randomized to receive absorbable hyaluronan hydrogel in one side as treated and the opposite side without absorbable hyaluronan hydrogel as control. Clinical outcome measures were assessed at postoperative 1, 2, 4, 8, and 12 weeks.*

Results: *Fifty-four patients completed the study. Overall, absorbable hyaluronan hydrogel significantly promotes the reepithelization process and reduces the presence of obstructing synechia, nonobstructing synechia, edema, crust, and mild mucopurulent drainage (all $p \leq 0.0002$). At all postoperative follow-up visits, the promotion in reepithelization is statistically significant at 2, 4, and 8 weeks, and the reductions in the presence of nonobstructing synechia, edema, crust, and mild mucopurulent drainage are all statistically significant except for the presence of crust at 12 weeks and mild mucopurulent drainage at 1 and 12 weeks. Although the presence of obstructing synechia at each follow-up visit between groups does not reach statistical significance, the incidence ranges from 5.56 to 12.96% in the control group and from 0 to 3.70% in the treated group. No adverse event related to treatment was observed.*

Conclusion: *In this clinical study, data analyses suggest that this new absorbable hyaluronan hydrogel, as nasal dressing/packing after ESS is safe and promotes the postoperative reepithelization process and reduces the presence of synechia, edema, crust, and mild mucopurulent drainage.*

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Despite the advances in instrumentation and surgical technique, poor wound healing after endoscopic sinus surgery (ESS) is still a significant problem. Postoperative debridement is routinely performed to manage scar/synechia formation but with limited success. Although currently various nasal dressings/packings have been developed, most of them have not been shown to have a significant impact in wound healing, and, even worse, some of them may in fact elicit a foreign body inflammatory response and actually promote scarring.[1–5]

Hyaluronan (HA) is a nonsulfated glycosaminoglycan found in the extracellular matrix of all vertebrate tissues, which plays a multifunctional role in scar-free wound healing.[6–9] However, the uses of unmodified HA in many clinical applications are restricted due to its major limitations of fluid nature and rapid *in vivo* degradation. Recently, these disadvantages had been overcome through our novel crosslinking/modification technology and new HA hydrogels had been shown excellent biocompatibility and great potential in wound healing and tissue regeneration.[10–15] In the previous study,[16] two new HA hydrogels (a rapid-gelling hydrogel and a preformed hydrogel) had been specifically designed and synthesized as nasal dressings, and the preformed HA hydrogel showed encouraging outcomes in promoting wound healing and preserving neo-ostium opening in a rabbit maxillary sinus model when compared with the control of nontreatment or Merogel (Medtronic Xomed Surgical Products, Jacksonville, FL) treatment.

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Here, a prospective, randomized, controlled study was conducted to assess the safety and efficacy of this preformed HA hydrogel (PureRegen Gel Sinus) after ESS.

MATERIALS AND METHODS

The study protocol was reviewed and approved by the Medical Ethics Board at both Shanghai Ninth People's Hospital (study ID 2010-16) and Shanghai Renji Hospital (study ID 2010-59).

Study Design

A prospective, randomized, controlled trial with blinded evaluation of the clinical outcome measures was conducted. Determined by randomization schedule after ESS, the patient was randomized to receive PureRegen Gel Sinus to either their left or right surgical cavity with the opposite side without PureRegen Gel Sinus serving as the control. Neither the patient nor the surgeon was blinded to the allocation.

Study Materials

PureRegen Gel Sinus is a new absorbable crosslinked HA hydrogel and was provided in a sterile prefilled glass syringe (BioRegen Biomedical, Changzhou, China).

Sample Size

The sample size was determined to be 54 patients (108 surgical cavities) to obtain at least 90% power ($\alpha = 0.05$) with the anticipated no more than 10% loss of patients in follow-ups and an assumed difference of 4.8 weeks (SD, 3 weeks) in the reepithelization time between the treated and control groups.[17]

Participants and Selection Criteria

Patients were recruited among those undergoing ESS for bilateral chronic rhinosinusitis (CRS) with bilateral polyposis, and informed consents were obtained from each participant. Inclusion criteria included a Lund-MacKay computed tomography scan score[18] of ≥6 on each side and an age of 18–65 years. Exclusion

criteria included (1) a known hypersensitivity to HA; (2) systemic diseases including serious hypertension, pulmonary tuberculosis, diabetes mellitus, hepatopathy, *etc.*; (3) abnormal liver and/or kidney functions; and (4) pregnancy or expecting to be pregnant within 6 months or lactating.

Intervention

Four surgeons were involved in the surgical intervention with one in one center and three in the other center. The bilateral ESS similar to the method reported by Berlucchi *et al*.[19] was performed on all patients with powered instrumentation while removing the polyposis on both sides and preserving the middle turbinates bilaterally and normal mucosa when possible. After completion of the surgery, all patients were randomized to receive nasal packing/dressings. In one side (treated group), PureRegen Gel Sinus (2 mL) was filled into the surgical cavity first and then the gelatin sponge or Sorbalgon (Paul Hartmann AG, Heidenhein, Germany) was placed into the surgical cavity and, finally, Merocel (Medtronic Xomed,) was placed in the middle meatus; in the opposite side (control group), the same packing/dressings were used but omitting PureRegen Gel Sinus.

On postoperative day 2, the Merocel and gelatin sponge/Sorbalgon was removed on both sides and any blood or mucus was suctioned, and then PureRegen Gel Sinus (2 mL) was refilled in the treated side while the control side was left empty. At that time, the patient was instructed to use normal saline spray in both nostrils 10–15 times/day to keep nasal passages moist. On postoperative day 7, any PureRegen Gel Sinus residue in the treated side was irrigated and any blood or mucus was suctioned in both sides in the office. At that time, the patient was instructed to begin twice-a-day nasal irrigation with normal saline using a bulb syringe, and the patient was also started on a topical aqueous nasal steroid spray. Patients were placed on antibiotics intraoperatively and were continued for 10 days postoperatively.

Outcome Measures

At postoperative 1, 2, 4, 8, and 12 weeks, the patients were evaluated in the office by an observer who was blinded to the treatment using 0 or 30° endoscopes. Treatment interventions were performed at these visits, including lysis of synechia, *etc*. Seven outcomes were assessed according to the "Diagnosis and Therapy Guideline of CRS in China (2008)."[20] Reepithelization range was evaluated as <10, 10–90, and >90% of the surgically removed mucosa area, and the reepithelization process was defined as primary outcome. The presence of nonobstructing synechia (absence or presence), obstructing synechia (absence, mild, or gross), edema (absence, mild, or gross), crust (absence, mild, or gross), mucus (absence, mild, or gross mucopurulent drainage), and polyposis (absence, presence in or beyond the middle meatus) were defined as secondary outcomes.[20]

The aforementioned outcome measures applied in this study are similar to those reported by Berlucchi *et al*.[19] To better assess the postoperative scar tissue formation, the presence of synechia was further evaluated as obstructing or nonobstructing and the latter refers to the presence of scar tissues only on the mucosal surface that does not block the pathways of the sinuses.

Statistical Analysis

All randomized patients who started treatment were included in analysis according to the intent-to-treat principle. All analyses were performed by using the SAS 9.2 Statistical Software package (SAS Institute, Cary, NC). When appropriate, Mantel-Cox test, Cochran-Mantel-Haenszel test, Fisher's exact test, paired *t*-test, or Wilcoxon rank sum test was performed for the analysis of efficacy outcomes in overall or between groups at different follow-up visits, and $p < 0.05$ was considered statistically significant.

RESULTS

Between August 2010 and September 2011 55 patients of bilateral CRS with bilateral polyposis were recruited, had bilateral ESS, and all completed at least one follow-up visit (Table 1), which were all included in the safety set population and full analysis set (FAS) based on intention-to-treat principle. One patient discontinued with reasons unrelated to the treatment, and the other 54 patients who completed all follow-up visits were included in the per protocol set (PPS). In this study, intention-to-treat analysis yielded results similar to the per protocol results; therefore, only the results from the PPS-based analyses were presented in the tables.

In this study there was no difference between before and after treatment, in the laboratory examination of blood and urine, that was with clinical meaning or related to PureRegen Gel Sinus and also there was no reported adverse event related to the treatment.

Gross Observation

The gross observation reveals that the PureRegen Gel Sinus treatment obviously improved postoperative wound healing. Faster reepithelization and less presence of scar tissue and bullae, *etc.*, were observed in the treated sides than in the control sides (pictures not shown).

Primary Outcome Measures

The reepithelization is shown in Table 2 (PPS-based analyses). Overall, the PureRegen Gel Sinus treatment significantly promoted the mucosal reepithelization process ($p < 0.0001$). Furthermore, at all follow-up visits, the mucosal reepithelization in the treated group was better than that in the control group, which is statistically significant at postoperative 2, 4, and 8 weeks ($p = 0.004$–0.0142). A similar result was obtained in the FAS-based analyses.

Secondary Outcome Measures

The presence of obstructing synechia is shown in Table 3 (PPS-based analyses). The incidences in the treated group were negligible at all follow-up visits (0–3.70%) compared with the control group which was at least three times higher at the same time points (5.56–11.96%). Although at each follow-up visit the incidence between groups was not significant ($p > 0.05$), overall, the obstructing syn-

Table 1 **Patient demographic characteristics**

Patients Enrolled	Age (yr)	Sex		Treated Side	
		Male	Female	Right	Left
55	44.80 ± 12.38* (20~64)#	43 (78.18%)	12 (21.82%)	28 (50.91%)	27 (49.08%)

**Mean ± SD.*
#Min ~ Max.

Table 2 **Reepithelization at postoperative wk 2, 4, 8, and 12***

Time (wk)	Group	Patient No. (percentage) with Different Reepithelization Range			Z#	p Value#
		>90%	10–90%	<10%		
1	Treated	0 (0.0%)	8 (14.8%)	46 (85.2%)	1.5775	0.1147
	Control	0 (0.0%)	3 (5.6%)	51 (94.4%)		
2	Treated	5 (9.3%)	33 (61.1%)	16 (29.6%)	3.5727	0.0004
	Control	1 (1.9%)	19 (35.2%)	34 (63.0%)		
4	Treated	28 (51.9%)	19 (35.2%)	7 (13.0%)	3.4959	0.0005
	Control	9 (16.7%)	32 (59.3%)	13 (24.1%)		
8	Treated	45 (83.3%)	7 (13.0%)	2 (3.7%)	2.4520	0.0142
	Control	33 (61.1%)	19 (35.2%)	2 (3.7%)		
12	Treated	52 (96.3%)	2 (3.7%)	0 (0.0%)	0.8285	0.4074
	Control	50 (92.6%)	4 (7.4%)	0 (0.0%)		
In overall (Mantel-Cox test): $Q_{CMH} = 30.9943$, $p < 0.0001$						

**PPS-based analyses.*
#Wilcoxon rank sum test between groups at different follow-up visits, Z = test statistic.
PPS = per protocol set.

Table 3 **The presence of obstructing synechia at postoperative wk 1, 2, 4, 8, and 12*#**

Time (wk)	1	2	4	8	12	Average
Control	11.11%	12.96%	9.26%	5.56%	7.41%	9.26
Treated	3.70%	1.85%	1.85%	1.85%	0%	1.85
In overall (CMH test)§: $\chi^2 = 14.0604$, $p = 0.0002$						

**PPS-based analyses.*
#$p > 0.05$ between groups at each postoperative week.
§Pooled analysis stratified by time.
CMH = Cochran-Mantel-Haenszel; PPS = per protocol set.

echia was significantly reduced in the treated groups ($p = 0.0002$). A similar result was obtained in FAS-based analyses.

The presence of nonobstructing synechia is shown in Table 4 (PPS-based analyses). In overall or at all follow-up visits, significantly less nonobstructing synechia was observed in the treated group with $p <$ 0.0001 or = 0.001–0.0459, respectively. A similar result was obtained in FAS-based analyses.

The presence of mucosal edema is shown in Table 5 (PPS-based analyses). In overall or at all follow-up visits, the mucosal edema was significantly lessened in the treated group with $p < 0.0001$ or =0.0000–0.0031, respectively. A similar result was obtained in FAS-based analyses.

The presence of crust is shown in Table 6 (PPS-based analyses). At 12 weeks postoperatively the crust was similar in both groups; however, in

Table 4 **The presence of nonobstructing synechia at postoperative wk 1, 2, 4, 8, and 12***

Time (wk)	Group	Patient Percentage with Different Nonobstructing Synechia			Z	p Value#
		Absence	Mild	Gross		
1	Treated	90.7%	9.3%	0%	1.9963	0.0459
	Control	77.4%	13.2%	9.4%		
2	Treated	83.3%	16.7	0%	2.3481	0.0189
	Control	64.8%	25.9%	9.3%		
4	Treated	79.6%	20.4%	0%	4.1052	0.0000
	Control	40.7%	59.3%	0%		
8	Treated	68.5%	31.5%	0%	3.5384	0.0004
	Control	35.2%	61.1%	3.7%		
12	Treated	79.6%	20.4%	0%	2.8756	0.0040
	Control	53.7%	44.4%	1.9%		
In overall (CMH test)§: $\chi^2 = 47.7661$, $p = 0.0000$						

**PPS-based analyses.*
#Wilcoxon rank sum test between groups at different follow-up visits.
§Pooled analysis stratified by time.
CMH = Cochran-Mantel-Haenszel; PPS = per protocol set.

Table 5 **Edema at postoperative wk 1, 2, 4, 8, and 12***

Time (wk)	Group	Patient Percentage with Different Edema			Z	p Value#
		Absence	Mild	Gross		
1	Treated	1.9%	92.6%	5.6%	5.4876	0.0000
	Control	0%	46.3%	53.7%		
2	Treated	31.5%	68.5%	0%	5.2212	0.0000
	Control	0%	81.5%	18.5%		
4	Treated	72.2%	27.8%	0%	5.0330	0.0000
	Control	24.5%	67.9%	7.6%		
8	Treated	88.9%	11.1%	0%	4.0188	0.0001
	Control	53.7%	46.3%	0%		
12	Treated	92.6%	7.4%	0%	2.9542	0.0031
	Control	70.4%	29.6%	0%		
In overall (CMH test)§: $\chi^2 = 105.2558$, $p = 0.0000$						

**PPS-based analyses.*
#Wilcoxon rank sum test between groups at different follow-up visits.
§Pooled analysis stratified by time.
CMH = Cochran-Mantel-Haenszel; PPS = per protocol set.

Table 6 **Crust at postoperative wk 1, 2, 4, 8, and 12***

Time (wk)	Group	Patient Percentage with Different Crust			Z	p Value#
		Absence	Mild	Gross		
1	Treated	46.3%	50.0%	3.7%	4.4913	0.0000
	Control	20.4%	35.2%	44.4%		
2	Treated	70.4%	27.8%	1.9%	3.8702	0.0001
	Control	37.0%	40.7%	22.2%		
4	Treated	88.9%	11.1%	0%	2.5920	0.0095
	Control	68.5%	29.6%	1.9%		
8	Treated	96.3%	3.7%	0.0%	1.9765	0.0481
	Control	85.2%	14.8%	0%		
12	Treated	96.2%	3.8%	0%	0.0097	0.9923
	Control	96.2%	3.8%	0%		
In overall (CMH test)§: $\chi^2 = 46.4148$, $p = 0.0000$						

**PPS-based analyses.*
#Wilcoxon rank sum test between groups at different follow-up visits.
§Pooled analysis stratified by time.
CMH = Cochran-Mantel-Haenszel; PPS = per protocol set.

overall or at postoperative 1, 2, 4, and 8 weeks significantly less crust was observed in the treated group with $p < 0.0001$ or =0.0000–0.0481, respectively. A similar result was obtained in FAS-based analyses.

No gross mucopurulent drainage was observed in both groups at all follow-up visits. The presence of mild mucopurulent drainage is shown in Table 7 (PPS-based analyses). In overall or at postoperative 2, 4, and 8 weeks, this mild mucopurulent drainage was significantly less in the treated group with $p < 0.0001$ or =0.0000–0.0047, respectively. A similar result was obtained in FAS-based analyses.

The presence of polyposis at all follow-up visits was similar and negligible in both groups, and no polyposis was observed in any of the patients at the last follow-up visit (12 weeks postoperatively).

Table 7 **The presence of mild mucopurulent drainage*#**

Time (wk)	1	2	4	8	12
Control	83.3%	83.3%	77.8%	64.8%	31.5%
Treated	83.3%	50.0%	50.0%	23.7%	25.4%
p Value§	1.0000	0.0004	0.0047	0.0000	0.5197
In overall (CMH test)¶: $\chi^2 = 31.8084$, $p = 0.0000$					

**PPS-based analyses.*
#No gross mucopurulent drainage was observed in any patients.
§Fisher's exact test between groups at different follow-up visits.
¶Pooled analysis stratified by time.
CMH = Cochran-Mantel-Haenszel; PPS = per protocol set.

DISCUSSION

Nonabsorbable nasal dressings/packings have been widely used to prevent postoperative bleeding; however, recent clinical studies have revealed that they had no efficacy in improving wound healing, and, even worse, might cause some adverse effects if they were not removed shortly after surgery.[1–5]

Absorbable nasal dressings/packings have the advantage of no removal and have been studied more recently. However, most of them still have not been shown to have a significant impact on the promotion of wound healing.[19,21–33] The studies performed by Chandra *et al*.[21,22] indicate FloSeal (Baxter International, Inc., Deerfield, IL) appears to be associated with scar tissue formation and may be incorporated into recovering mucosa and increase the degree of postoperative care. A randomized, controlled prospective study of 27 patients undergoing ESS for bilateral CRS performed by Kastl *et al*.[23] reveals that carboxymethylcellulose nasal packing (ArthroCare, Glenfield, U.K.) has no appreciable effect on wound healing when compared with no treatment. A prospective, double-blinded, randomized trial of 30 patients undergoing ESS for bilateral CRS performed by Shoman *et al*.[24] reveals that NasoPore (Stryker Canada, Hamilton, ON, Canada) does not significantly reduce the risk of bleeding or patient discomfort and is associated with significantly slower mucosal healing initially when compared with a Merocel placed in a vinyl glove finger. More recently, in a randomized controlled trial of 40 patients undergoing ESS for bilateral CRS, chitosan/dextran gel treatment shows significantly fewer adhesions and rapid hemostasis but with no significant difference in crusting, mucosal edema, infection, or granulation tissue formation when compared with no treatment.[25]

HA is believed to be an ideal material in nasal dressings because of its excellent biocompatibility and multifunctional role in scar-free wound healing, such as scavenging reactive oxygen species, enhancing wound reepithelialization, modulating inflammatory response and stimulating angiogenesis by its degraded fragments, and markedly reducing fibrous scarring in fetal wounds, *etc*.[6–9,34] Currently, two leading absorbable nasal dressings, dispensed gel particles of crosslinked HA (Sepragel; Genzyme Biosurgery, Ridgefield, NJ) and nonwoven of benzyl esterified HA (Merogel), are both made from HA through crosslinking/modification technologies.[19,26–33] However, the crosslinking/modification technologies should be carefully selected and precisely controlled, otherwise the unique capability of HA in scar-free wound healing may be compromised and even causing inflammation, *etc.* For instance there are many controversial reports concerning the safety and efficacy of Merogel in both animal and clinical studies.[19,26–32] A multicenter, prospective, randomized, controlled trail of 66 patients undergoing ESS for unilateral or bilateral CRS performed by Berlucchi *et al*.[19] suggested that when compared with Merocel the treatment of MeroGel significantly reduced nasal adhesions at postoperative weeks 4 and 12 ($p = 0.041$ and <0.001, respectively) but with no reduction at postoperative week 2, significantly reduced the presence of granulation at postoperative week 4 ($p < 0.001$) but not significant at postoperative week 12 ($p = 0.058$), insignificantly improved reepithelization at postoperative weeks 4 and 12 with no improvement at postoperative week 2, and had no improvement in the presence of crusting and mucosal edema ($p = 0.247$–0.345). However, in animal[26–29] and other clinical studies,[30–32] MeroGel was reported to cause extensive fibrosis, may have osteogenic potential, and have no significant difference in adhesion formation or the microscopic features of wound healing, when compared with no treatment or Merocel control. On the other hand, using a different crosslinking/modification technology, Sepragel shows better potential in promoting wound healing when compared with no treatment in a single-blinded, randomized, controlled trial of 10 patients undergoing ESS for bilateral CRS.[33] In the 5-week postoperative follow-up visits, Sepragel significantly reduced synechia and middle meatal stenosis at 2–5 weeks, significantly reduced mucosal edema at 2–4 weeks but with no improvement at 5 weeks ($p = 0.5634$ or 0.6092), and significantly improved reepitheliazation at 2–4 weeks but with no improvement at 5 weeks ($p = 0.8384$ or 0.8822).

PureRegen Gel Sinus evaluated in this study is a new crosslinked HA hydrogel developed through our novel crosslinking/modification technology, and this hydrogel has been precisely designed and optimized to give a suitable retention and absorption time in the wounded sinuses without hurting the biocompatibility and capability in improving scar-free wound healing of HA.[16] The preclinical animal study in a rabbit maxillary sinus model suggests PureRegen Gel Sinus has significant better potential in promoting wound healing and preserving neo-ostium opening when compared with the control of no treatment or Merogel treatment.[16] Therefore, PureRegen Gel Sinus is expected to promote wound healing after ESS.

In this prospective, randomized, controlled trial, 55 patients undergoing bilateral ESS were enrolled and 54 patients completed the whole study. After surgery, the same temporary nasal packing/dressings (Merocel and gelatin sponge/Sorbalgon) were placed on both sides to prevent postoperative bleeding and were both removed shortly after surgery (at postoperative day 2) to avoid the potential adverse effects caused by remaining in the cavity for an extensive time period.[19,24,30] Therefore, the only difference between treated and control sides was receiving PureRegen Gel Sinus or not. Seven clinical outcome measures were assessed at follow-up visits at postoperative weeks 1, 2, 4, 8, and 12.

Data analyses suggest that, overall, PureRegen Gel Sinus significantly promotes the mucosal reepithelization process ($p < 0.0001$; Table 2) and significantly reduces the presence of obstructing synechia ($p = 0.0002$; Table 3), nonobstructing synechia ($p < 0.0001$; Table 4), edema ($p < 0.0001$; Table 5), crusting ($p < 0.0001$; Table 6), and mild mucopurulent drainage ($p < 0.0001$; Table 7). Moreover, data analyses suggest that between groups the promotion in reepithelization was significant at postoperative weeks 2, 4, and 8 with $p = 0.004$–0.0142 (Table 2), and the reductions in nonobstructing synechia, edema, and crusting were all significant at all postoperative follow-up visits of 1, 2, 4, 8, and 12 weeks (except for crusting at 12 weeks) with $p = 0.000$–0.0459, 0.0000–0.0031, and 0.0000–0.0481, respectively (Tables 4–6). PureRegen Gel Sinus treatment also significantly reduced the mild mucopurulent drainage at postoperative weeks 2, 4, and 8 ($p = 0.0000$–0.0047; Table 7), which might be the result of better and faster wound healing in the treated group.

In this study the results of PureRegen Gel Sinus treatment seem quite encouraging in promoting wound healing after ESS. However, caution should be taken when comparing these results with those reported in other studies because of the variability in surgeons, different clinical trial design, and the objective assessment of the clinical outcome measurements though currently they are widely used in the clinical studies after ESS.

CONCLUSION

In this prospective, multicenter, randomized, controlled trial, data analyses suggest PureRegen Gel Sinus as nasal dressing/packing after ESS is safe and promotes the postoperative reepithelization process and reduces the postoperative presence of synechia (obstructing and nonobstructing), edema, crusting, and mild mucopurulent drainage.

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