The clinical outcomes of using a new cross-linked hyaluronan gel in endoscopic frontal sinus surgery

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Abstract In endoscopic sinus surgery (ESS) synechiae formation and ostial stenosis are frequently encountered. This is not uncommon after frontal recess and ostium interventions due to the narrow recess and difficult anatomy of the region. The goal of this study is to evaluate the efficacy of the new cross-linked hyaluronan gel—PureRegen® Gel Sinus—on wound healing and synechiae prevention in endoscopic frontal sinus surgery. The study consists of two groups of patients who underwent ESS, including frontal sinus surgery. In the study group of 37 patients, PureRegen® Gel Sinus was applied to both the frontal recess and ostium at the end of the procedure. The control group consisted of 28 patients. In this group, nasal dressing material was not applied at the end of surgery—neither to the frontal recess nor to the ostium. Postoperatively, epithelization was found to be significantly better at 2 and 4 weeks in the study group when compared with the findings in patients where no postoperative dressing was applied. In the eighth week, there was no significant difference found between the two groups in terms of epithelization. Synechiae formation was significantly lower in the PureRegen® Gel Sinus group than the control group at all 2, 4 and 8 weeks postoperative evaluations. The effects of PureRegen® Gel Sinus on wound healing, especially in reepithelialization, have shown to occur earlier in the postoperative period. Rapid reepithelialization and control of infection related granulation tissue formation with antibiotics in the early postoperative period may explain the low stenosis rate in frontal sinus ostia in PureRegen® Gel Sinus applied patients.

Keywords Endoscopic sinus surgery · Frontal sinus · Nasal packing · Synechiae · Hyaluronan · PureRegen® Gel Sinus

Introduction

The formation of synechiae is one of the most common and important complications after endoscopic frontal sinus surgery (EFSS) [1]. During EFSS the involved sinuses are subjected to extirpation of mucosa and bone to enlarge sinus ostia and/or remove obstructions. Because of the proximity of denuded surfaces and the presence of clot, the restructured sinus anatomy is prone to subsequent development of synechiae, ostial stenosis and scar contraction [2]. Various techniques and materials have been introduced to prevent synechiae formation such as the insertion of physical barriers, which includes different types of packing, stents, drug eluting stents, as well as repeated postoperative debridement and irrigation to remove eschars, crusts and blood clots. Resection or medialization of the middle turbinate, mucosal flaps and mucosa sparing instrument technologies has also been developed to address this. Postoperative systemic or topical corticosteroids and steroid eluting stents [1] have also been used to prevent the development of granulation and scar tissue. However, none of these exertions have been proven to be totally effective in the prevention of synechiae formation, especially in a narrow frontal recess and in the ostium. The idea of viscoseparation which refers to the interposition of highly viscous and elastic bio-materials between denuded surfaces...
was first introduced about 15 years ago [2]. This technique is applied to prevent the formation of fibrin connections and subsequent ingrowth of fibroblasts. Highly purified, high molecular weight hyaluronic acid molecules (hyaluronans) have been developed and used experimentally to decrease adhesion formations between various denuded surfaces. The resulting new polymers, generically called hylans, have been cross-linked to form water insoluble gels (hylan B) to increase residence time. Hylan B gels have been developed for use as barrier substances to prevent adhesions and excessive scar formation in the sinus cavity [2]. PureRegen® Gel Sinus is a new cross-linked hyaluronan (HA) gel developed using proprietary thiolated chemistry. The modification/crosslinking is precisely regulated so that the cross-linked HA gel has an adequate degradation profile and viscosity. PureRegen® Gel is able to survive in the implantation space and stay in position for about 2 weeks to cover the critical period of tissue repair. This is due to its high, dynamic viscosity (more than 100,000 mPa/s) that is about ten-times higher than that of original HA materials, and also much higher than that for HA gels composed of dispersed cross-linked particles. The raw HA material used for the production of PureRegen® Gel Sinus is the result of a fermentation process used to avoid the potential immune rejection of xenogeneic protein, and other inflammatory reactions that could occur with animal extracted HA material. A comprehensive biocompatibility study based on ISO 10993 guidelines was performed on PureRegen® Gel Sinus. All results indicated that PureRegen® Gel Sinus is biocompatible. The positive effects of PureRegen® on postoperative wound healing and synechiae prevention in sinus cavities was also reported in a recent study by Shi et al. [3] and Matheny et al. [4]. In this retrospective clinical study, PureRegen® Gel Sinus was investigated for its efficacy and safety to promote wound healing and prevent synechiae, especially in the frontal recess and the ostium area after EFSS.

Materials and methods

The senior author has been performing endoscopic frontal sinus surgery in different pathologies of frontal recess and sinuses for 20 years. The preferred operating technique is an endoscopic approach under visualization with 45° and 70° telescopes. The bony cell walls in the frontal recess area are gently removed with various frontal recess giraffe forceps, cutting forceps and curved microdebrider blades when needed. Computer assisted image guidance has also been used in select cases. At the end of the operation different dressing materials like Nasopore, Spongostan or Merocel were applied only to the middle meatus to control bleeding when indicated. Before the introduction of PureRegen® Gel Sinus, no surgical dressing material, which may cause fibrosis or synechiae, was applied directly to the frontal recess and ostium area in endoscopic frontal sinus surgery patients, mainly because of the difficulty in accessing this area, removing the materials there postoperatively and patient discomfort in doing these manipulations. After January 2015, PureRegen® Gel Sinus became available and the authors began using it as a wound dressing material in the frontal recess and ostium area at the end of EFSS operations. Besides the primary purpose, which was prevention of synechiae, filling the sinus cavity with this highly viscous gel was also helpful for mild oozing. In the study group, hemostatic materials like Nasopore, Spongostan or Merocel were also applied only to the middle meatus when indicated. On postoperative follow-up of patients where PureRegen Gel was applied, better healing results with fewer frontal recess fibrosis and synechiae formation was clinically observed. A retrospective study for evaluation of this observation was planned as prospective clinical studies are prohibited in private hospitals in Turkey. Furthermore, it was important to not increase the risk of synechiae in newly performed cases by not using the PureRegen Gel. The cases performed in the last 12 months before the introduction of this new gel were selected as controls to provide the closest possible match to the study group in terms of surgical technique and expertise.

In this study, postoperative follow-up findings of EFSS patients where PureRegen® Gel Sinus was applied directly to the frontal ostium and frontal recess (study group) were compared with the findings of EFSS patients whom were operated between January 2014 and 2015. In this control group, no dressing material to neither the frontal recess nor to the ostium was used to address the potential of reepithelization and synechiae formation. Only patients with chronic frontal sinus inflammation, mucosal thickening in frontal recess and frontal ostium blockage without polyps were included in the study to minimize variables.

In the study group, 5 ml PureRegen® Gel Sinus (BioRegen Biomedical Co., Ltd., Changzhou, Jiangsu, China) was applied to each side of the frontal ostium and frontal recess area with a curved sinus suction tube attached to the luer lock syringe at the end of the procedure (Fig. 1a, b).

All patients received postoperative instructions, which included: avoid nose blowing, maintain the head in an elevated position during rest and sleeping, avoid heavy lifting and sport activities for 14 days. In the early postoperative period gently moisturizing nasal passages with saline nasal sprays three to four times a day was recommended and saline irrigation started after the 7th day of the surgery. All patients were prescribed antibiotics (cefuroxime axetil 500 mg BID) for 10 days.
As PureRegen® Gel is sustainable and keeps its position in the implanted space for about 2 weeks. Sinus cavities were not cleaned in the first 2 weeks postoperatively. At 2 weeks postoperatively, blood clots, dried mucus and gel remnants—if applied—were cleaned from the middle meatus and frontal recess in all patients. Any debris was also gently removed from the frontal ostium with curved suction cannulas. This procedure not only provided evaluation of the operation site, but it also helped prevent infection and related granulation tissue formation and fibrosis.

After the procedure, all patients were followed-up for 2 months in biweekly intervals with endoscopic examinations. Results were recorded and documented according to our clinic’s endoscopic sinus surgery (ESS) follow-up protocol (Fig. 1c, d).

All operations were performed by the same surgeon, (the senior author) using the same operation room settings, and the same surgical dissection technique was applied to each patient. Pathologic tissues in ethmoid sinuses were excised with different angled power instruments and frontal recesses were dissected with giraffe and through cutting frontal forceps with the preservation of normal looking mucosa as much as possible. A Draf type 1 sinusotomy was performed, and circumferential excision and stripping of the mucosa in the frontal recesses and ostiums were avoided as much as possible in all cases.

During follow-up visits, 2, 4 and 8 weeks postoperatively, patients were examined with 0° and 70° telescopes with a Storz Telepack X Led system to assess wound healing and synechiae formation in the frontal recess and frontal ostium. The status of healing with epithelization of the frontal recess and ostium were scored as 1: none, 2: moderate with ostium narrowing and 3: serious with ostium blockage.

All statistical analysis was performed with SPSS 23 Software. Independent samples t test was used to compare epithelization and synechiae formation between study and control groups at the second, fourth and eighth week. Statistical significance was set at $P < 0.05$.

**Results**

In the study group, 37 patients underwent EFSS between January 2015 and December 2015, to open blocked frontal sinus ostium. In this group, 25 patients were male and 12 patients were female, with a mean age of 37.8 (24–76). Bilateral EFSS was performed on 27 patients, while unilateral was done on 10 patients. (a total of 64 sites).

In the control group, 28 patients underwent EFSS between January 2014 and 2015. In this group, 19 patients were male and nine patients were female, with a mean age of 42.9 (26–63). Unilateral EFSS was performed in seven patients and bilateral was done on 21 patients (a total of 49 sites).

The statistical analysis of the study group postoperative follow-up data showed that the epithelization was significantly better at the second and fourth week when PureRegen® Gel Sinus was applied. No significant difference was found between the two groups in terms of epithelization 8 weeks postoperatively (Table 1). However, synechiae formation was found to be significantly lower at all postoperative examinations—2, 4 and 8 weeks—when PureRegen® Gel Sinus was applied (Table 2).
Endoscopic sinus surgery (ESS) is one of the most frequently performed operations in the otorhinolaryngology specialty. In ESS, postoperative care and prevention of synechiae formation, especially in narrow frontal recess and frontal ostium areas are as important as performing proper surgical techniques to obtain successful, long term results.

There are many different non-absorbable and absorbable nasal dressing materials used in ESS to provide hemostasis, prevent postoperative adhesions and promote wound healing. Although absorbable dressing materials have advantages such as no need for removal and less patient
discomfort, most of them have not yet shown to have a significant positive effect on tissue healing [5–8]. An absorbable packing material, FloSeal (Baxter Int. Inc., Deerfield, IL) has shown to be associated with scar tissue formation and a prolonged postoperative care period as discussed by Chandre et al. [8]. In another study, Kastl et al. [9] reported that carboxymethyl cellulose nasal packing (ArtroCare, Glenfield, UK) has no significant positive effect on wound healing. Shoman et al. reveal that one of the most preferred absorbable nasal packing materials, NasoPore (Stryker Canada, Hamilton, ON, Canada) is associated with significant delay in mucosal healing when compared to Merocel, placed in a Vinyl glove finger [10]. In a randomized, controlled trial of 40 patients, Valentine et al. reported that chitosan/dextran gel provides significantly fewer adhesions, but has no significant positive effect on crusting, mucosal edema, infection or granulation tissue formation in ESS for bilateral chronic sinusitis [11].

HA-derived dressing materials MeroGel and Sepragel (Genzyme Biosurgery, Ridgefield, NJ) provide excellent biocompatibility and enhancing effects on the reepithelization of sinus cavities while reducing fibrosis and preventing scar formation [2]. Franklin and Wright reported early wound healing without any inappropriate osteoneogenesis and osteitis in ESS patients with MeroGel [12], but Miller et al. found no difference in synechiae formation in ESS patients with the same dressing material [13].

PureRegen Gel Sinus, which is a new cross-linked HA hydrogel developed through a novel crosslinking technology, has been designed and optimized to give a suitable retention and absorption time in sinuses after endoscopic surgery without harming the biocompatibility and scar-free wound healing capability of HA [14]. Chen et al. reported significantly better potential in promoting wound healing and preserving the neo-ostium opening when using PureRegen Gel Sinus compared to Merogel, or not applying any dressing material in a preclinical animal study in rabbits [15]. In a recent prospective, multicenter, randomized study with 54 patients, Shi et al. reported significantly promoted reepithelization and reduced obstructing synechiae with PureRegen Gel Sinus at 2, 4 and 8 weeks after ESS, compared to a group in which no dressing material has been used [3]. Matheny et al. compared PureRegen® gel Sinus with Stammberger foam in a randomized study [4]. Biopsy tissue samples were collected from the ethmoid cavity at 12 weeks after surgery and the mucociliary regeneration was observed and scored under a microscope. It was reported that the synechiae was significantly less in the PureRegen® gel group than in the Stammberger group. PureRegen® gel demonstrated the ability to facilitate mucociliary regeneration.

Before the introduction of PureRegen® Gel Sinus, synechiae formation, the occurrence of granulation, infection and a prolonged healing period were the primary observed problems in our practice. This was especially true in patients with frontal recess and frontal ostium interventions. After the initiation of PureRegen® applications to the frontal ostium, frontal recess and ethmoidal cavity, significant improvements were observed in terms of duration and the quality of wound healing clinically.

In previous studies, the effects of PureRegen® Gel Sinus on postoperative epithelization and the prevention of synechiae was evaluated in ESS patients. However, no specific data were presented about the effects of this material on the healing of the frontal recess and frontal ostium areas, which are the most challenging and problematic sites in ESS. In this retrospective clinical study, we evaluated the potency of PureRegen® Gel Sinus on reepithelization and the prevention of synechiae formation especially in the narrow frontal recess and frontal ostium areas.

In our study, reepithelization of frontal recess and ostium was found to be significantly better in the group where PureRegen® was applied at the second (P = 0.020) and fourth (P = 0.001) week. No significant difference was observed between the groups at eighth week (P = 0.431). This result reveals that after sinus surgery, wound healing with reepithelization finalizes in the eighth week in most patients with or without PureRegen Gel Sinus application, but the process is significantly faster and finalizes mostly in the first 4-week period with less fibrosis and synechiae formation when PureRegen® Gel Sinus is applied, which effects the final outcomes.

When comparing the degree of fibrosis and synechiae formation in the frontal recess and frontal ostium areas, we found significantly lower scores in the study group in all second (P = 0.013), fourth (P = 0.021) and eighth (P = 0.009) week observations. Total closure of frontal ostium with fibrosis and synechiae formation was observed in three patients in control group and one patient in PureRegen group on 8theighth-week follow-up. Opening of the closed ostiums with Draf type 2 a or b procedures were performed in all these patients. Secondary cases were not included in the study.

These results reveal that in patients where PureRegen® Gel Sinus is applied most of the reepithelization occurs in postoperatively in 4 weeks’ time. Faster reepithelization of denuded bony surfaces prevents secondary infections, granulation tissue formation and fibrosis and synechiae. In the first 10 days of the postoperative period, prevention of wound infection with antibiotics may likely help the promoting effect of PureRegen® Gel Sinus on wound healing, which eventually helps prevent scar and synechiae formation throughout the rest of the healing period.
Conclusion

This retrospective clinical study analyses of the data shows the promoting effects of PureRegen® Gel Sinus on the early reepithelization and wound healing in sinus cavities after endoscopic frontal sinus surgery. Furthermore, in cases where PureRegen® Gel Sinus is applied less fibrosis and synechiae formation in the frontal recess and ostium area was observed. This finding can be related to the prevention of infection and granulation tissue formation with early reepithelization of denuded bony surfaces in the frontal recess and ostium after surgery. Antibiotic treatment in the early postoperative period may also help the effect of the gel by preventing infection. These outcomes need to be confirmed in laboratory and clinical trials with histological tissue evaluations.

References