




The postoperative outcomes of patients with chronic rhinosinusitis with nasal polyps by sustained released steroid from hyaluronic acid gel

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Abstract

Purpose The self-crosslinked hyaluronic acid (scHA) and steroids are considered as efficient factors for postoperative management after chronic rhinosinusitis (CRS) nasal surgery. This randomized clinical trial is designed to investigate the efficacy and potential of scHA gel as a topical drug sustained release carrier for steroid of budesonide.

Methods The study is performed with 30 patients of chronic rhinosinusitis with nasal polyps (CRSwNP) who underwent functional endoscopic sinus surgery (FESS). The single application of scHA was assessed in the control patient group for postoperative recovery. In the treatment patient group, the combination of scHA/budesonide was applied for postoperative management. The patients are followed up in 2 weeks, 4 weeks and 12 weeks after surgery.

Results The combination of scHA/budesonide results in better endoscopic scoring and mucus evaluation than the single scHA application.

Conclusion The results indicate that the combination of scHA/budesonide is a valuable treatment for the FESS postoperative management and implies the potential of scHA gel as a topical drug sustained release scaffold.

Keywords Self-crosslinked hyaluronic acid · Budesonide · Chronic rhinosinusitis · Functional endoscopic sinus surgery · Topical sustained release

Introduction

Chronic rhinosinusitis (CRS), including chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP), is most commonly treated disease in the otolaryngology departments in hospitals [9]. CRS is attributed to multifactorial causes such as environmental factors and host characteristics [28]. It affects approximately 10–15% of the Western population [22] and 8% of the Chinese population [23]. CRS results in serious health consequences and health-related quality of life [22, 23].

Currently, the functional endoscopic sinus surgery (FESS) is more and more often used to improve the prognosis of CRS patients. FESS on the CRSwNP patients generates greater wound in nasal cavity and is more interesting to be investigated. The postoperative complications such as nasal adhesions is an often cause of endoscopic sinus surgery failure, resulting in poorer outcomes and a higher likelihood of revision surgery [21], with adverse effects on patients' health-related quality of life scores [14]. Thus, the postoperative management methods are needed to be further investigated.

Hyaluronic acid (HA) is a biological material, which exists in extracellular matrix. The unique hygroscopic, viscoelastic and mucoadhesive capability, the high immunological and toxicological safety of HA have led to its broad application in ENT surgery, gynecological surgery, orthopedical surgery, general surgery and cosmetic surgery [4]. The modulating effect of HA in wound healing and mucosal regeneration has been demonstrated in clinical trials following nasal surgery, in which safety, tolerability and efficacy of HA were reported [10]. However, the uses of unmodified

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HA in many clinical applications are inconvenient due to its fluid nature and/or ineffective due to its rapid in vivo degradation with a short half-life of 0.5–3 days [11]. In order to overcome these disadvantages, modification of HA such as the crosslinking of natural HA to high-molecular weight HA is the strategy for better and broader clinical applications.

Recently, a novel self-crosslinked HA (scHA) hydrogel had been specifically designed and synthesized as a nasal dressing. It fulfills the criteria of a good nasal dressing. First of all, it and its degraded fragments are safe. Secondly, it is capable to promote a scar-free wound healing. Additionally, it provides a suitable retention and absorption time in wounded sinuses due to selectively and precisely controlled self-crosslinking modification technology. The previous studies show that this scHA hydrogel convincingly improves postoperative recovery, promotes wound healing and prevents nasal synechia after FESS [3, 5, 19, 24].

CRS is primarily inflammatory disease involving nasal mucosa [1]. Therefore, oral and topical steroids remain critical components of postoperative management of CRS. Oral steroids are commonly used for acute sinusitis exacerbations but are poorly suited for long-term therapy due to their systemic side effects. Topical steroid application currently plays a vital role in maintenance therapy for patients with CRS due to their ease of use and tolerability. However, these medications may not be effective for patients with inflammation localized to the frontal or sphenoid sinuses, anatomic regions that are difficult to reach with sprays and irrigations. Nasal steroid sprays may not deliver adequate amounts of medication to the entire postoperative nasal and sinus cavity because of polyposis, mucosal edema, secretions, scarring and crusting after FESS. It is necessary to develop more advanced drug delivery system from biomaterials that could be used in postoperative processes.

Materials and methods

The study protocols involving human participants are in accordance with the ethical standards of the institutional ethics committee and with the Helsinki Declaration.

Materials

PureRegen[®] Gel Sinus is a new absorbable self-crosslinked hyaluronic acid hydrogel (scHA) and was provided in a 5-ml glass syringe (BioRegen Biomedical Co., Ltd., Changzhou, China). In related experiments, 1 ml of budesonide (AstraZeneca, Co., Ltd., Shanghai, China) is pre-mixed with 5 ml of PureRegen[®] sinus gel to a final concentration of 0.17 mg/ml.

Patient recruitment

In this randomized controlled clinical trial, 30 of CRSwNP patients including four females and 26 males aged 29–73 years old were recruited. Patients were diagnosed according to the EPOS-2007 criteria [9]. Clinical information including age, gender, course of disease, coexistence of allergic rhinitis, surgical history, antibiotic allergy smoking status and preoperative computed tomography (CT) examination were recorded prior to surgery. Inclusion criteria included a Lund-MacKay CT scan ≥ 6 on each side [17]. Exclusion criteria included (1) hypersensitivity to HA; (2) systemic diseases such as serious hypertension, pulmonary tuberculosis, diabetes mellitus, hepatopathy; (3) regular use of hormones (4) pregnancy or expecting to be pregnant within 12 months or lactating.

Study design

Bilateral FESS was performed on all patients. Patients underwent surgeries from July 2018 to December 2018 at the Department of Otolaryngology of the Affiliated Eye, Ear, Nose and Throat Hospital of Fudan University as previously described [7, 13, 16, 30]. At the end of the surgery, the random chosen side of sinus cavity was filled with PureRegen[®] sinus gel (the scHA group), and the other side of sinus cavity was filled with PureRegen[®] sinus gel pre-mixed with budesonide (final concentration of 0.17 mg/ml) (the scHA/Bu group).

Outcomes measurement

After surgery, all patients were followed up for 3 months with endoscopic examinations at second, fourth and 12th week. The patients were evaluated by a surgeon who is blind to this study.

Six outcomes were assessed. The Lund-Kennedy endoscopic scores were assessed as previously described [7, 13, 16, 30], and this endoscopic scoring was defined as primary outcome. The presences of mucus (absence, mild, severe), edema (0–10), crust (absence, mild, severe), scar (absence, presence) and polyposis (absence, presence) were defined as secondary outcomes.

Statistical analysis

Statistical analyses were carried out using SAS 9.3 (SAS Inc., USA). The data are presented as mean \pm standard deviation (SD). The differences were analyzed by the paired samples *t* test among groups. The Wilcoxon

signed-rank test was employed for data with skewed distribution. $p < 0.05$ was used to indicate a significant difference.

Results

Basic characteristics

A total of 30 patients with CRS were enrolled in the study. All patients are CRSwNP disease. Clinical information were recorded prior to surgery, including age, gender, course of disease, coexistence of allergic rhinitis, surgical history, antibiotic allergy and smoking status. The basic characteristics are documented in Table 1.

The basic information shows that patients are randomly collected samples which are in line with the inclusion and exclusion criteria of this study design.

The combination of self-crosslinked hyaluronan/budesonide (scHA/Bu) improves endoscopic scores comparing to self-crosslinked hyaluronan (scHA)

The pre-surgical endoscopic scores of patients group treated with the combination of self-crosslinked HA/budesonide (scHA/Bu group) (mean = 3.27) and patients group treated with self-crosslinked HA (scHA group) (mean = 3.37) were in the same region without significant differences ($p = 0.5099$).

The pre-surgical Lund-MacKay CT scores of scHA/Bu group (mean = 7.77) and scHA group (mean = 8.07) were in the same region without significant differences ($p = 0.5450$).

The patients were followed up at second, fourth, and 12th week after surgery, and the endoscopic scores were evaluated. The endoscopic scores at the fourth week from both scHA/Bu group and scHA groups are listed in Table 2. Reference source not found. The results show that the endoscopic scores between scHA/Bu group (mean = 1.51)

Table 1 Characteristics of patients

Item	Proportion or mean \pm SD
Age (years)	52.85 \pm 11.44
Gender (F/M)	4/26
Course of CRSwNP (years)	6.11 \pm 8.52
Allergic rhinitis (+/-)	16/14
History of sinus surgery (+/-)	7/23
Antibiotic allergy (+/-)	0/30
Smoking (+/-)	15/15

In the study, 30 patients with CRSwNP disease were recruited. The clinical information are documented and listed in the table. SD standard deviation

Table 2 Endoscopic scores at the fourth week follow-up after surgery

Patient group	N	Mean	SD	Minimum	Maximum
scHA/Bu	30	1.51	0.14	0.00	4.00
scHA	30	1.97	0.22	0.00	4.00

The endoscopic scores from 30 patients (N) treated with the combination of scHA/budesonide (scHA/Bu) or scHA alone (scHA) were evaluated. SD standard deviation

and scHA group (mean = 1.97) are significantly different ($p = 0.03134$). Figure 1 shows the mean and the corresponding 95% confidence interval in both groups.

Actually, the endoscopic scores were already clearly improved at the second week follow-up in the scHA/Bu group (mean = 1.87) compared to the scHA group (mean = 2.33) although it is not statistically significant ($p = 0.1381$) due to the variation from the limited patient number. At the 12th week follow-up, there is no significant differences ($p = 0.5018$) between scHA/Bu group (mean = 1.17) and scHA group (mean = 1.33) due to the possible reason that all patients were recovered from the surgery.

The combination of scHA/Bu reduces mucus compared to scHA

The pre-surgical mucus evaluation of patients in the scHA/Bu group (mean = 0.73) and scHA group (mean = 0.87) is comparable without significant differences ($p = 0.3594$). The patients were followed up at second, fourth, and 12th week after surgery, and mucus data were evaluated.

At the second week follow-up, the mucus values of scHA/Bu group and scHA groups are listed in Table 3. Reference source not found. It is found that the values in scHA/

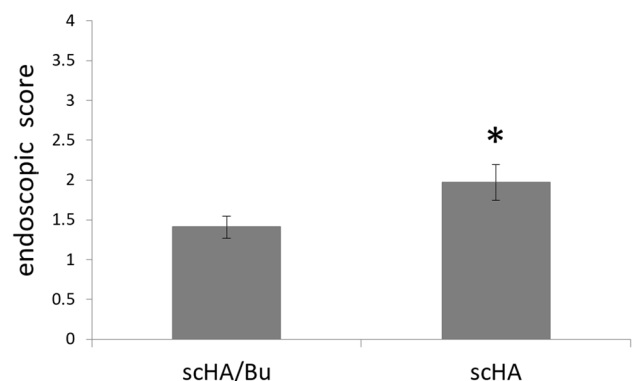


Fig. 1 Endoscopic scores at the fourth week follow-up after surgery. The endoscopic scores from 30 patients treated with the combination of scHA/budesonide (HA/Bu) or scHA alone (scHA) were evaluated. Mean and 95% confidence interval of endoscopic score are shown in the diagram (*, $p < 0.05$)

Table 3 Mucus evaluation at the second week follow-up after surgery

Patient group	N	Mean	SD	Minimum	Maximum
scHA/Bu	30	0.70	0.12	0.00	2.00
scHA	30	1.03	0.13	0.00	2.00

The values from the 30 patients (*N*) treated with the combination of scHA/budesonide (scHA/Bu) or scHA alone (scHA) are documented and listed in the table

SD standard deviation

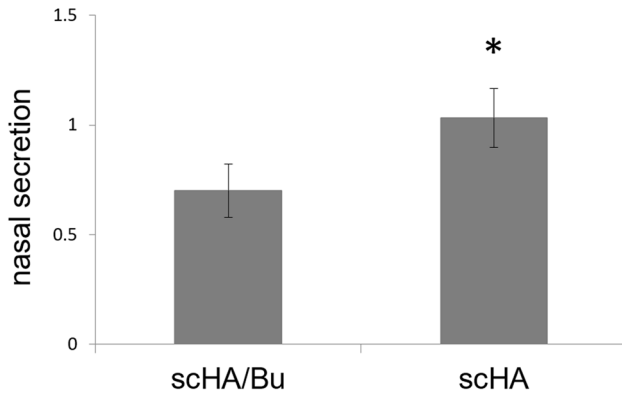


Fig. 2 Mucus evaluation at the second week follow-up after surgery. The values were collected from 30 patients treated with the combination of scHA/budesonide (scHA/Bu) or scHA alone (scHA). Mean and 95% confidence interval of scores are shown in the figure (*, $p < 0.05$)

Bu group (mean = 0.70) and scHA group (mean = 1.03) are significantly different ($p = 0.0472$). The mean and the corresponding 95% confidence interval in both groups are shown in Fig. 2.

As expected, the mucus values were continually improved at fourth week follow-up in scHA/Bu group (mean = 0.6) compared to the scHA group (mean = 0.8) although it is not statistically significant ($p = 0.3137$) due to the variation from the limited patients sample size. At the 12th week follow-up, there is no significant differences ($p = 0.68$) between scHA/Bu group (mean = 0.53) and scHA group (mean = 0.60) due to the possible reason that all patients were recovered from the surgery.

The combination of scHA/Bu has the similar effects on edema, crust, scar and polyposis compared to scHA

The secondary outcome data such as edema, crust, scar and polyposis were measured and statistically analyzed as well. All of the data do not show statistically significant differences between scHA/Bu group and the scHA group.

Discussion

CRS is a prevalent disease in otolaryngology. Data show that two types of CRS, i.e., CRSsNP and CRSwNP, are partially differently behaving at the symptom level and molecular levels [15, 16, 25, 29]. In practices, more severity, more recurrence and more complication often happen in CRSwNP patients [6], which are chosen to be the main focus of the current study.

CRS is often clinically treated through FESS. The postoperative management is very important for the quality of life of patients and reduction in revision surgery. So far, more suitable postoperative methods are still required for comfortably postoperative recovery of patients.

As expected, this study shows that both self-crosslinked HA(scHA) and the combination of scHA/Budesonide lead to the significantly improved endoscopic scoring compared to pre-operational values (data not shown). Though the surgery itself plays the major role, scHA is surely assumed to contribute to the postoperative recovery process, which are supported by several previous studies [5, 19, 24].

There are several data which show that the topical steroid therapy in nasal cavity is a good handling after FESS with the function of reducing inflammation and promoting wound healing [18, 27]. As a note, the current topical therapy is mainly using rinse or spray, which have several disadvantages such as inaccurate steroid concentration, difficulty to reach the right nasal position and short-term steroid release. An ideal topical treatment system or a drug delivery system should be an absorbable, controlled, sustained release of medication to the affected mucosa, as well as adhesion prevention and maintenance of ostial patency.

This study investigated if the scHA could be used as a carrier for the sustained release of steroids. Indeed, the data show that the combination of scHA/budesonide has improved effects on the postoperative recovery on nasal endoscopic scoring and nasal mucus. In addition, *in vitro* releasing experiments show that scHA extends the time duration of 80% release of steroid from 2 days (48 h) to nearly 2 weeks (312 h) comparing to the nasal packing material Nasopore (data not shown). This *in vitro* data are in line with the time period in this study when the significant effects of endoscopic scores and mucus are observed. Considering that Nasopore is associated with significant delay in mucosal healing [26], we assume that HA is an optimal material for both functional wound regeneration and sustained release of drugs in postoperative management.

It is known that budesonide is effective to decrease the edema in FESS postoperative management [8, 12]. Meanwhile, several studies show that HA decreases

postoperative edema as well [2, 20, 24]. Though the combination of HA/budesonide does not show the additive effects on improvement of nasal edema in this study than the single application of HA, it is still worth for being recommended for the postoperative recovery due to its effects on endoscopic scoring and mucus.

Our study is showing that some early results of a HA-based steroid delivery system may play an increasingly important role in comfortable postoperative recovery. These topic steroid delivery systems are still needed to be continually investigated, and long-term outcomes are needed to be assessed.

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Data availability Available.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The study was approved by Ethics committee of The Eye, Ear, Nose and Throat Hospital of Fudan University, Shanghai, China. The approval number is 20170010-1.

Consent to participate All authors agree to participate in this study.

Consent for publication All authors agree to publish this study.

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