The efficacy of a novel budesonide chitosan gel on wound healing following endoscopic sinus surgery

Thanh Ha, MBBS[1], Rowan Valentine, MBBS[1], Stephen Moratti, PhD[2], Lyall Hanton, PhD[2], Simon Robinson, FRACS[3] and Peter-John Wormald, MD[1]

Background: **Adhesion formation and ostial stenosis are common causes of surgical failure after endoscopic sinus surgery (ESS). Postoperative topical steroid application has been shown to improve wound healing. Chitosan-dextran gel (CD gel) is an effective hemostatic nasal dressing. This study aims to determine the effect of the addition of budesonide to CD gel on postoperative ostial stenosis and adhesion formation following ESS.**

Methods: **This prospective, blinded, randomized controlled trial was conducted between October 2012 and April 2015. Thirty-six patients over 18 years undergoing ESS were randomized to receive either: no treatment, CD gel, CD gel with 1 mg/ 2 mL budesonide, or topical steroid cream to their left or right sinuses (different treatment each side). Each sinus ostium and endoscopic features of wound healing was measured intraoperation, and 2 weeks, 3 months, and 12 months postoperation.**

Results: **Data was analyzed using the analysis of variance (ANOVA) and post hoc Tukey honestly significant difference (HSD) tests. There was a significant reduction in stenosis within all 3 sinuses ostia sites when CD + budesonide was compared to control, with the greatest effect seen at 12 months: The mean ± standard deviation (SD) percentage of baseline areas at 12 months were 76% ± 6.2% vs 37% ± 23.5%, 76% ± 6.3% vs 52% ± 4.9%, and 83% ± 6.5% vs 58% ± 5.0% (all $p < 0.05$), for CD + budesonide compared to control in the frontal, sphenoid, and maxillary sinuses, respectively. The incidence of adhesions was 4% in the CD + budesonide group compared to 15% in the control group.**

Conclusion: **This study has shown that CD gel, when combined with topical budesonide solution, improves long-term sinus ostial patency and prevents ostial stenosis post-ESS.**

Key Words:
endoscopic sinus surgery; chitosan; dextran; adhesion; chronic rhinosinusitis; healing

***How to Cite this Article*:**
Ha T, Valentine R, Moratti S, Hanton L, Robinson S, Wormald PJ. The efficacy of a novel budesonide chitosan gel on wound healing following endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2017;XX:1-9.

Endoscopic sinus surgery (ESS) is the treatment of choice for chronic rhinosinusitis (CRS) refractory to maximal medical therapy.[1–3] Ongoing bleeding and adhesion formation remain the 2 most common complications following surgery.[4] Additionally, scaring and adhesion formation is 1 of the main causes of surgical failure, estimated to occur in between 10% and 30% of patients.[5] The incidence of ostial stenosis following ESS has also been estimated to be approximately 25%.[3] The frontal sinus has the highest rate of stenosis, with rates reported of up to 59.5%.[6,7] The frontal sinus is particularly prone toward stenosis due to its narrow size, close adjacent surrounding structures such as the skull base and orbit, and residual bony septations after surgery.[8–11]

Removable nasal packing has been the traditional method of preventing adhesion formation following ESS. However, it is rated by patients as the most unpleasant and painful aspect of the ESS experience,[12] and is associated with significant mucosal trauma as the pack is removed.[13]

[1]*Department of Surgery–Otorhinolaryngology, Head and Neck Surgery, University of Adelaide, Adelaide, Australia;* [2]*Department of Chemistry, University of Otago, Dunedin New Zealand;* [3]*Wakefield Nasal and Sinus Institute, Wakefield Hospital, Wellington, New Zealand*

Correspondence to: Peter-John Wormald, MD, Department of Otorhinolaryngology, Head and Neck Surgery, Queen Elizabeth Hospital, 28 Woodville Road, Woodville, SA 5011, Australia; e-mail: peterj.wormald@adelaide.edu.au

Funding sources for the study: Garnett Passe and Rodney Williams Memorial Foundation; The University of Adelaide.
Potential conflict of interest: S.M., L.H., S.R., and P.J.W. have patented the use of chitosan dextran gel in the nose after surgery.

Received: 30 August 2016; Revised: 30 October 2017; Accepted: 30 October 2017
DOI: 10.1002/alr.22057
View this article online at wileyonlinelibrary.com.

Novel absorbable nasal packing agents have been developed in recent years but have not shown a significant decrease in adhesion formation.[14,15]

In order to reduce the incidence of stenosis and adhesions, a number of intraoperative and postoperative techniques have been developed to achieve more rapid re-epithelialization and reciliation. Intraoperative techniques include mucosal sparing by the use of through-cutting instruments and microdebriders.[16] Other surgeons advocate an intensive postoperative treatment regime with frequent endoscopic debridements, topical nasal steroids, and nasal irrigation. Whether adhesion formation and scaring ultimately occurs depends on the delicate balance between fibrinolysis and fibroblast-initiated collagen deposition, thought to be controlled by clot formation and fibrinous exudate secreted at the wound site.[17,18]

Topical steroid application in the postoperative setting has been shown to improve wound healing, including reducing edema, fibrin deposition, and granulation tissue formation.[19–21] However, delivery of topical steroids can be difficult, particularly in applying the steroid to the operative site, and keeping it in contact with the mucosa.

Within the field of otorhinolaryngology chitosan-dextran gel (CD gel) has been shown to be an effective postoperative absorbable nasal dressing. It is also an effective hemostat that improves the microscopic and macroscopic features of wound healing.[22–24] Postoperative ostial stenosis has also been investigated with the use of CD gel. CD gel significantly improved sinus ostial patency. The largest difference was seen when ostial areas at 12 weeks were compared with their corresponding baseline areas (66% vs 31% frontal, $p < 0.001$; 85% vs 47% sphenoid, $p < 0.001$; and 74% vs 54% maxillary ostia, $p = 0.002$).[25]

With the success of CD gel in preventing ostial stenosis, this study aims to determine the effect of the addition of budesonide to CD gel on the healing of the sinuses and on postoperative ostial stenosis. Also in this study, the effect of CD gel with budesonide is compared against topical steroid alone in order to clarify whether any difference is due to the steroid in isolation or in combination with CD components.

Patients and methods

Inclusion/exclusion criteria

This prospective, blinded, randomized controlled trial was granted ethics approval from the tertiary teaching hospital ethics committee. This study was conducted between October 2012 and April 2015. Patients undergoing bilateral functional ESS for CRS, and who were >18 years of age were invited to participate in this study. Exclusion criteria were allergy to shellfish, pregnancy or breastfeeding, or asymmetrical surgery.

Study design

All eligible patients gave informed consent. Demographic information and details of the procedure were recorded for each patient. All patients underwent bilateral complete ESS using meticulous mucosal sparing techniques with powered instrumentation. All patients underwent complete bilateral frontal recess clearance, maxillary antrostomy, anterior and posterior ethmoidectomies, and sphenoidotomies.

Patients were randomized using the letter/envelope method to receive either: no treatment on 1 side and CD gel on the other side (groups 1A and 1B), CD gel on 1 side and CD gel with 1 mg/2 mL budesonide (Pulmicort Respules®; AstraZeneca AB, Sodertalje, Sweden) on the other side (groups 2A and 2B), or CD gel with 1 mg/2 mL budesonide on 1 side and topical steroid cream (0.1% betamethasone valerate) on the other side (groups 3A and 3B). The side of treatment was also randomized (Table 1).

After completion of bilateral surgery, each sinus ostia was measured with a standardized specifically designed measurement probe, as described.[25] As per the randomized group allocation, either 8 mL of CD gel mixed with 2 mL of budesonide solution (total budesonide dose = 1 mg, total volume of CD + budesonide = 10 mL), or 10 mL of CD gel only, or 10 mL of topical betamethasone, or nothing was applied to the surgical site including the middle meatus, frontal recess, fovea ethmoidalis, and sphenoid ostium.

Postoperatively all patients received a course of antibiotics, and were instructed to perform saline douches 4 times daily on each side starting on the day after surgery. All patients received postoperative intranasal steroids. Budesonide in saline 240-mL douches (budesonide ampule 1 mg/2 mL) were commenced on average 16 days after surgery (95% confidence interval, 1.6 days) and continued daily for study period.

Patients were reviewed at 2 weeks, 3 months, and 12 months postoperatively. During each postoperative visit, rigid nasendoscopy was performed and recorded. Patients underwent routine debridement of both nasal cavities at these visits as required. Ostial measurements were performed using the standardized, custom designed ostial measurement probe, as described.[25] Each postoperative video was then evaluated by a blinded observer to measure ostial size and endoscopic features of wound healing (adhesion presence and severity, mucosal edema, granulation tissue formation, evidence of pus, and crusting; Table 2). Postoperative ostial sizes were compared against intraoperative measurements, ensuring that each frame of video demonstrated a full view of the entire perimeters of both the ostia and the ball probe placed precisely at the adjacent perimeter of the ostium. Features of wound healing were graded using an ordinal visual analogue scale (VAS). The severity of adhesions were graded based on the percentage of the vertical height of the middle turbinate taken up by the adhesion.

Statistical methods

The results of ostial area measurements were compared between treatment groups at each of 4 time points:

TABLE 1. Patient distribution for each of groups 1A, 1B, 2A, 2B, 3A, and 3B*

Group	Left sinus	Right sinus	Patients in subgroup (n)	Patients with nasal polyps (n)	Patients undergoing revision surgery (n)	Total patients in group (n)
Group 1[a]						13
1A	Control (nothing)	CD gel	6	3	4	
1B	CD gel	Control (nothing)	7	3	4	
Group 2[b]						12
2A	CD gel	CD gel with budesonide	5	3	3	
2B	CD gel with budesonide	CD gel	7	4	5	
Group 3[c]						11
3A	CD gel with budesonide	Steroid only	5	2	3	
3B	Steroid only	CD gel with budesonide	6	3	4	

*Total number of patients recruited = 40, excluded = 4. Total remaining in study = 36, each with 2 sets of sinuses (left and right).
[a]Group 1: Control on 1 side, CD gel on the other side.
[b]Group 2: CD gel on 1 side, CD with budesonide on the other side.
[c]Group 3: CD with budesonide on 1 side, steroid only on the other side.
CD = chitosan-dextran.

TABLE 2. Baseline intraoperative areas for frontal, sphenoid, and maxillary ostia*

Area	Control	CD gel	*p*[a]	CD gel with budesonide	*p*[a]	Steroid only	*p*[a]
Frontal	37.6 ± 7.37	39.3 ± 12.47	0.766	37.4 ± 7.46	0.970	37.9 ± 8.35	0.836
Sphenoid	126.4 ± 9.95	129.7 ± 7.10	0.631	128.8 ± 6.01	0.751	127.1 ± 8.05	0.840
Maxillary	198.1 ± 7.90	201.8 ± 7.56	0.254	200.5 ± 6.36	0.326	203.1 ± 6.19	0.272

*Values are mean ± SD mm^2.
[a]Values of *p* compare each group with control.
CD = chitosan-dextran; SD = standard deviation.

TABLE 3. Percentage of baseline intraoperative areas for frontal ostia at 2 weeks, 3 months, and 12 months postoperation*

	Control (%)	CD gel (%)	CD gel with budesonide (%)	Steroid only (%)	CD gel vs control (*p*)	CD gel vs CD with budesonide (*p*)	CD with budesonide vs steroid only (*p*)
2 weeks	57 ± 5.3	40 ± 19.3	64 ± 5.9	23 ± 20.4	0.145	0.0001	0.001
3 months	33 ± 18.2	67 ± 6.6	68 ± 7.0	30 ± 18.6	0.001	0.899	0.001
12 months	37 ± 23.5	64 ± 5.9	76 ± 6.2	33 ± 18.6	0.001	0.013	0.001

*Values are mean ± SD.
CD = chitosan-dextran; SD = standard deviation.

intraoperation for baseline measurements (Table 2), and postoperation at 2 weeks, 3 months, and 12 months (Tables 3–5). These were collated to produce a mean value with standard deviations, in mm^2 for original intraoperative measurements and as a percentage for each postoperative time point. Data for ostial measurements were analyzed using an analysis of variance (ANOVA) statistical model with "treatment" defined as control ("A"), CD only ("B"), CD with budesonide ("C"), or steroid only ("D"). Where the *p* value corresponding to the F-statistic of the ANOVA analysis was lower than 0.05, suggesting that 1 or more of the treatments are significantly different, post hoc Tukey honestly significant difference (HSD) analysis was applied to determine which of the pairs of treatments were

TABLE 4. Percentage of baseline intraoperative areas for sphenoid ostia at 2 weeks, 3 months, and 12 months postoperation*

	Control (%)	CD gel (%)	CD gel with budesonide (%)	Steroid only (%)	CD gel vs control (*p*)	CD gel vs CD with budesonide (*p*)	CD with budesonide vs steroid only (*p*)
2 weeks	33 ± 6.7	57 ± 5.9	67 ± 5.2	25 ± 24.1	0.001	0.007	0.001
3 months	43 ± 6.4	80 ± 6.1	83 ± 7.7	44 ± 16.8	0.001	0.59	0.001
12 months	52 ± 4.9	0.70 ± 6.1	76 ± 6.3	47 ± 7.2	0.001	0.009	0.001

*Values are mean ± SD.
CD = chitosan-dextran; SD = standard deviation.

TABLE 5. Percentage of baseline intraoperative areas for maxillary ostia at 2 weeks, 3 months, and 12 months postoperation*

	Control (%)	CD gel (%)	CD gel with budesonide (%)	Steroid only (%)	CD gel vs control (*p*)	CD gel vs CD with budesonide (*p*)	CD with budesonide vs steroid only (*p*)
2 weeks	67 ± 9.2	53 ± 5.9	76 ± 6.0	53 ± 7.6	0.001	0.001	0.001
3 months	52 ± 6.1	75 ± 8.0	78 ± 5.9	46 ± 6.6	0.001	0.49	0.001
12 months	58 ± 5.0	78 ± 7.6	83 ± 6.5	46 ± 6.4	0.001	0.058	0.001

*Values are mean ± SD.
CD = chitosan-dextran; SD = standard deviation.

significantly different from the other, in particular: control vs CD gel ("A"#"B"), CD gel vs CD with budesonide ("B"#"C"), and CD with budesonide vs steroid only ("C"#"D"), where k = 4, v = 68 degrees of freedom, and significance level was set at 0.05. Graphical representations are displayed in Figures 1–3, which plot the means for each treatment at each time point. The ordinal grading results for adhesions and wound healing (adhesions, edema, granulation tissue, pus, and crust formation) for each group were analyzed using chi-squared test for each of the 3 time points (Tables 6–10), with significance set at 0.05.

Results

A total of 40 patients were enrolled into the study, with patient ages ranging from 18 to 74 years, with a mean age of 46.4 years. All patients underwent complete bilateral functional ESS (FESS) procedures (maxillary antrostomy, sphenoethmoidectomy, and frontal sinusotomy). A total of 17 were primary operations, and 23 were revision surgeries. Four of the 40 recruited patients did not complete the full set of postoperative follow-up consultations, and therefore were subsequently excluded from the study. Of the 36 patients who remained in the study, 6 were randomized to group 1A, 7 were randomized to group 1B (total of 13 in group 1A and 1B combined), 5 were randomized to group 2A, 7 were randomized to group 2B (total of 12 in group 2A and 2B combined), 5 were randomized to group 3A, and 6 were randomized to group 3B (total of 11 in group 3A and 3B combined). This yielded a total of 72 individual sinus sides (36 patients with left and right sinus pairs each) that were distributed between control, CD gel only, CD + budesonide, and steroid only (Table 1).

Effect of CD gel, CD + budesonide, and steroid alone with regard to ostial stenosis

There was no significant difference in the mean values for intraoperative (baseline) frontal, maxillary, and sphenoid sinus ostia between treatment sides (Table 2).

Each sinus ostium was compared to its baseline size for each time point (as a percentage value, % ± standard deviation [SD]), presented in Table 3 for frontal ostia, Table 4 for sphenoid ostia and Table 5 for maxillary ostia).

Ostial sides that were treated with CD gel were compared against ostial sides that served as controls (received no treatment). Statistical significance was only demonstrated at 3 months and 12 months postoperation for frontal ostia. At 3 months, the mean size of "control" frontal ostia was 0.33 ± 0.182 mm^2 compared to the mean size of "CD gel" frontal ostia, which was 0.67 ± 0.066 mm^2 ($p = 0.001$). And at 12 months, the mean size of "control" frontal ostia was 0.37 ± 0.235 mm^2 compared to the mean size of "CD gel" frontal ostia 0.64 ± 0.059 mm^2 ($p = 0.001$). The difference between CD gel and control sides was significant at all time points for the sphenoid and maxillary ostia (Tables 2–5).

Ostial sides that were treated with CD+budesonide were compared against ostial sides that were treated with CD gel only (to determine the effect of adding steroid to the gel composition). Statistical significance was demonstrated at 2 weeks and 12 months postoperation for frontal and sphenoid ostia, but only significant at 2 weeks for

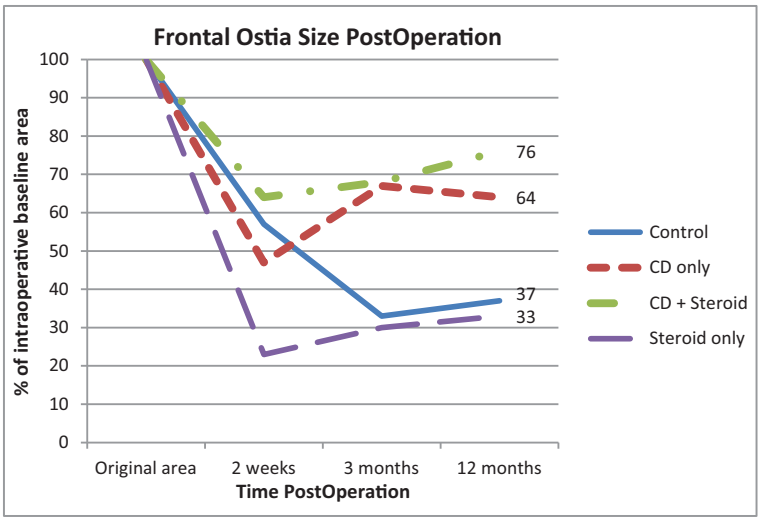

FIGURE 1. Graph comparing percentage of baseline area of frontal ostia for each group at 2 weeks, 3 months, and 12 months postoperation.

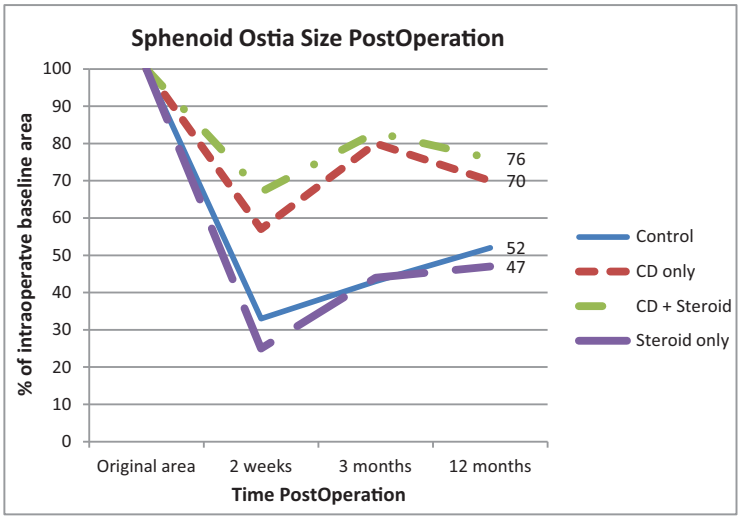

FIGURE 2. Graph comparing percentage of baseline area of sphenoid ostia for each group at 2 weeks, 3 months, and 12 months postoperation.

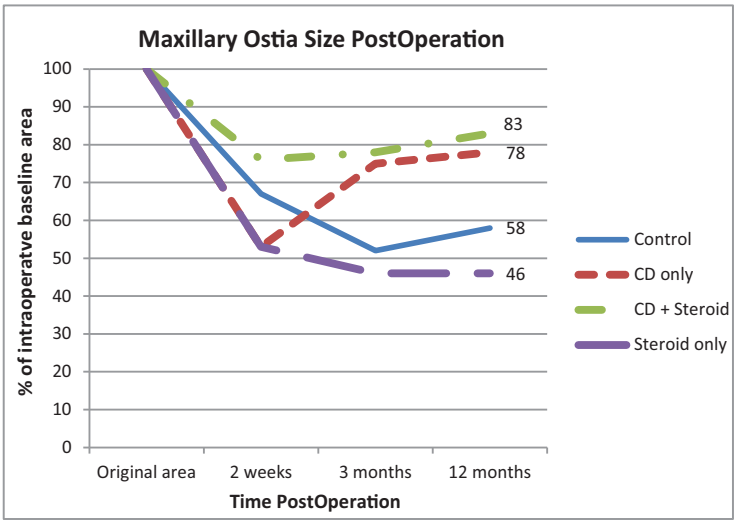

FIGURE 3. Graph comparing percentage of baseline area of maxillary ostia for each group at 2 weeks, 3 months, and 12 months postoperation.

TABLE 6. Incidence and severity of adhesions using an ordinal visual assessment scale (0 to 3) for each treatment at each time point

Time point	Adhesions	Control	CD gel	CD gel with budesonide	Steroid only
2 weeks	Grade 0, n	10	20	19	7
	Grade 1, n	0	0	1	1
	Grade 2, n	2	3	1	1
	Grade 3, n	1	2	2	2
	Incidence of adhesions, %	23	20	17	36
3 months	Grade 0, n	10	22	21	8
	Grade 1, n	1	1	0	2
	Grade 2, n	1	1	1	1
	Grade 3, n	1	1	1	1
	Incidence of adhesions, %	23	12	9	33
12 months	Grade 0, n	11	23	22	9
	Grade 1, n	0	1	0	0
	Grade 2, n	1	1	1	1
	Grade 3, n	1	0	0	1
	Incidence of adhesions, %	15	8	4	18

CD = chitosan-dextran.

TABLE 7. Incidence and severity of edema using an ordinal visual assessment scale (0 to 3) for each treatment at each time point

Time point	Edema	Control	CD gel	CD gel with budesonide	Steroid only
2 weeks	Grade 0, n	7	20	20	5
	Grade 1, n	1	1	1	1
	Grade 2, n	3	2	1	2
	Grade 3, n	2	2	1	3
	Incidence of edema, %	46	20	13	55
3 months	Grade 0, n	10	21	21	6
	Grade 1, n	0	1	0	1
	Grade 2, n	3	2	2	2
	Grade 3, n	2	1	1	2
	Incidence of edema, %	33	16	13	45
12 months	Grade 0, n	12	24	23	10
	Grade 1, n	0	0	1	0
	Grade 2, n	1	1	0	0
	Grade 3, n	0	0	0	1
	Incidence of edema, %	8	4	4	9

CD = chitosan-dextran.

TABLE 8. Incidence and severity of granulation tissue formation using an ordinal visual assessment scale (0 to 3) for each treatment at each time point

Time point	Granulations	Control	CD gel	CD gel with budesonide	Steroid only
2 weeks	Grade 0, n	10	23	22	8
	Grade 1, n	0	0	0	0
	Grade 2, n	2	1	1	1
	Grade 3, n	1	1	0	2
	Incidence of granulations, %	23	8	4	27
3 months	Grade 0, n	12	24	22	9
	Grade 1, n	0	0	0	0
	Grade 2, n	1	1	1	1
	Grade 3, n	0	0	0	1
	Incidence of granulations, %	8	4	4	18
12 months	Grade 0, n	12	24	22	9
	Grade 1, n	0	1	1	1
	Grade 2, n	1	0	0	0
	Grade 3, n	0	0	0	1
	Incidence of granulations, %	8	4	4	18

CD = chitosan-dextran.

TABLE 9. Evidence and severity of pus formation using an ordinal visual assessment scale (0 to 2) for each treatment at each time point

Time point	Pus	Control	CD gel	CD gel with budesonide	Steroid only
2 weeks	Grade 0, n	8	22	21	7
	Grade 1, n	2	1	1	2
	Grade 2, n	2	2	1	2
	Incidence of pus, %	33	12	9	36
3 months	Grade 0, n	11	22	22	8
	Grade 1, n	0	1	0	1
	Grade 2, n	2	2	1	2
	Incidence of pus, %	15	12	4	27
12 months	Grade 0, n	10	21	20	8
	Grade 1, n	2	3	3	2
	Grade 2, n	1	1	0	1
	Incidence of pus, %	23	16	14	27

CD = chitosan-dextran.

maxillary ostia. At 12 months, the mean size of "CD only" frontal ostia was 0.64 ± 0.059 mm^2 compared to the mean size of "CD+budesonide" frontal ostia, which was 0.76 ± 0.062 mm^2 ($p = 0.013$); and the mean size of "CD only" sphenoid ostia was 0.70 ± 0.061 mm^2 compared to the mean size of "CD + budesonide" sphenoid ostia, which was 0.76 ± 0.063 mm^2 ($p = 0.009$).

Ostial sides that were treated with steroid only were compared against ostial sides that were treated with CD + budesonide (to determine whether the effect was

TABLE 10. Incidence and severity of crust formation using an ordinal visual assessment scale (0 to 2) for each treatment at each time point

Time point	Crusts	Control	CD gel	CD gel with budesonide	Steroid only
2 weeks	Grade 0, n	9	18	19	6
	Grade 1, n	1	4	2	2
	Grade 2, n	3	3	2	3
	Incidence of crust formation, %	31	28	17	45
3 months	Grade 0, n	11	22	22	8
	Grade 1, n	1	1	1	1
	Grade 2, n	1	2	0	1
	Incidence of crust formation, %	15	12	4	20
12 months	Grade 0, n	12	24	23	9
	Grade 1, n	0	1	0	0
	Grade 2, n	1	0	0	1
	Incidence of crust formation, %	8	4	0	10

CD = chitosan-dextran.

attributable to the steroid only). Statistical significance was demonstrated at all time points for all 3 ostia. At 12 months, the mean size of "CD + budesonide" frontal ostia was 0.76 $\pm$ 0.062 mm^2 compared to the mean size of "steroid only" frontal ostia, which was 0.33 $\pm$ 0.186 mm^2 ($p = 0.001$); the mean size of "CD + budesonide" sphenoid ostia was 0.76 $\pm$ 0.063 mm^2 compared to the mean size of "steroid only" sphenoid ostia, which was 0.47 $\pm$ 0.072 mm^2 ($p = 0.001$); and the mean size of "CD + budesonide" maxillary ostia was 0.83 $\pm$ 0.065 mm^2 compared to the mean size of "steroid only" maxillary ostia, which was 0.46 $\pm$ 0.064 mm^2 ($p < 0.01$).

Effect of CD gel, CD + budesonide, and steroid alone with regard to adhesion formation

The incidence and severity of adhesions at 2 weeks, 3 months, and 12 months for each group are shown in Table 6. At 12 months postoperation, the incidence of adhesions was least in the CD with budesonide group (4%) compared to control (15%). The steroid-only group exhibited a higher incidence than control (18%). Of these, the adhesions were equally distributed between grades 2 and 3 for the control and steroid-only groups, compared with grade 1 and 2 for CD-only group and only 1 grade 2 for the CD+budesonide group.

Effect of CD gel, CD + budesonide, and steroid alone with regard to other features of wound healing

The incidence and severity of edema, granulation tissue, pus, and crust formation at 2 weeks, 3 months, and 12 months are shown in Tables 7–10 for each treatment group.

Discussion

Nasal packing materials are commonly used in the hope of improving wound healing outcomes for patients following ESS. CD gel alone has been demonstrated to significantly improve ostial stenosis following surgery compared to no treatment. This randomized controlled trial in 36 patients demonstrated that the addition of budesonide to CD gel when compared to CD gel alone, resulted in a significant reduction in ostial stenosis up to 12 months following surgery in frontal and sphenoid sinus ostia sites, but not in maxillary sites. When compared to control however, all 3 ostial sites demonstrated significance in reduction of ostial stenosis. Furthermore, there was a statistical significance for all 3 ostial sites when CD with budesonide was compared to topical betamethasone alone, indicating that the effect seen with the CD+budesonide combination is not due to the steroid effect alone.

Dissolvable dressings have been used primarily for hemostatic purposes immediately post-ESS. However, dressings that show good hemostatic properties[26–31] also increase postoperative scar formation.[14,26] This is because activation of the clotting cascade also serves to activate the inflammatory pathways that are detrimental to wound healing. Chandra et al.[14] showed that FloSeal significantly increased granulation formation ($p = 0.007$) and adhesion formation ($p = 0.006$), a finding continued to be observed at 21 months following surgery. These findings were also supported by work conducted by Shrime et al.,[26] and Maccabee et al.[15]

Chitosan is prepared from chitin, a polymer that is found naturally in crustaceans.[30] Chitosan is currently used ubiquitously as a preservative for foods, and as an antimicrobial coating on fruits and vegetables for human consumption as well as an additive to shampoos and toothpaste.[31] The specific chitosan derivative used in CD gel has shown positive results as a postoperative nasal dressing, as both an effective hemostat as well as anti-adhesion and anti-stenotic agent.[22] The mechanism by which CD gel prevents adhesion formation is not completely understood. It is likely that the chitosan component provides the haemostatic effect while the dextran component acts to inhibit fibroblast migration and proliferation, which allows re-epithelialization and reciliation to occur, and this takes place long enough to prevent collagen deposition and adhesion formation.[23] Recent studies[32],[33] on steroid-eluding implants have shown promise with a significant reduction in adhesion formation postoperatively; however, ostial sinus patency has not been assessed in those studies. The additional anti-stenotic effect seen with the CD+budesonide combination in this study suggests that the steroid component acts in synergy with the chitosan and dextran components to reduce early postoperative inflammation, and thereby further reducing fibroblastic migration and proliferation. The difference between groups with regard to features of wound healing has not shown statistical significance in this study. This result is likely due to the low total incidence of each feature. Despite the lack of significance, the clinical significance can be seen in the lower absolute incidence and lower severity of adhesions seen in the CD+budesonide group compared to both control and steroid-only groups.

Conclusion

The ability to potentially reduce inflammation postsurgery and to thereby improve wound healing by placing steroid in the operative field has been seen in steroid eluding devices. This study has shown that CD gel, when combined with budesonide, improves long-term sinus ostial patency and prevents ostial stenosis within the maxillary and sphenoid sinuses. In addition CD gel has been shown to have good hemostatic effects in the immediate postoperative period.

Acknowledgments

We thank the Garnett Passe and Rodney Williams Memorial Foundation and The University of Adelaide who provided funding for this project. We also thank Dr Ahmed Bassiouni, statistician. The work at the University of Otago was carried out as part of a Ministry for Business, Innovation and Employment (MBIE), NZ, contract UOOX1206. Prof. Brian Robinson had significant input to this project.

References

1. Kaliner MA, Osguthorpe JD, Fireman P, et al. Sinusitis: bench to bedside. Current findings, future directions. *Otolaryngol Head Neck Surg*. 1997;116:S1–S20.
2. Lazar RH, Younis RT, Long TE. Functional endonasal sinus surgery in adults and children. *Laryngoscope*. 1993;103:1–5.
3. Ramadan HH. Surgical causes of failure in endoscopic sinus surgery. *Laryngoscope*. 1999;109:27–29.
4. Gross RD, Sheridan MF, Burgess LP. Endoscopic sinus surgery complications in residency. *Laryngoscope*. 1997;107:1080–1085.
5. Wormald PJ. *Endoscopic Sinus Surgery: Anatomy, Three-Dimensional Reconstruction, and Surgical Technique*. New York: Thieme; 2005.
6. Jacobs JB. 100 years of frontal sinus surgery. *Laryngoscope*. 1997;107:1–36.
7. Hosemann W, Kuhnel T, Held P, Wagner W, Felderhoff A. Endonasal frontal sinusotomy in surgical management of chronic sinusitis: a critical evaluation. *Am J Rhinol*. 1997;11:1–9.
8. Friedman M, Landsberg R, Schults RA, Tanyeri H, Caldarelli DD. Frontal sinus surgery: endoscopic technique and preliminary results. *Am J Rhinol*. 2000;14:393–403.
9. Hunter B, Silva S, Youngs R, Saeed A, Varadarajan V. Long-term stenting for chronic frontal sinus disease: case series and literature review. *J Laryngol Otol*. 2010;124:1216–1222.
10. Casiano RR, Livingston JA. Endoscopic Lothrop procedure: the University of Miami experience. *Am J Rhinol*. 1998;12:335–339.
11. Becker DG, Moore D, Lindsey WH, Gross WE, Gross CW. Modified transnasal endoscopic Lothrop procedure: further considerations. *Laryngoscope*. 1995;105:1161–1166.
12. Chandra RK, Kern RC. Advantages and disadvantages of topical packing in endoscopic sinus surgery. *Curr Opin Otolaryngol Head Neck Surg*. 2004;12(1):21–26.
13. Shaw CL, Dymock RB, Cowin A, Wormald P-J. Effect of packing on the nasal mucosa of sheep. *J Laryngol Otol*. 2000;114:506–509.
14. Chandra RK, Conley DB, Haines GK 3rd, Kern RC. Long-term effects of FloSeal packing after endoscopic sinus surgery. *Am J Rhinol*. 2005;19:240–243.
15. Maccabee MS, Trune DR, Hwang PH. Effects of topically applied biomaterials on paranasal sinus mucosal healing. *Am J Rhinol*. 2003;17:203–207.
16. Wormald PJ. Salvage frontal sinus surgery: the endoscopic modified Lothrop procedure. *Laryngoscope*. 2003;113:276–283.
17. Davey AK, Maher PJ. Surgical adhesions: a timely update, a great challenge for the future. *J Minim Invasive Gynecol*. 2007;14(1):15–22.
18. Diamond MP, Decherney AH. Pathogenesis of adhesion formation/reformation: application to reproductive pelvic surgery. *Microsurgery*. 1987;8:103–107.
19. Hosemann W, Wigand ME, Gode U, Langer F, Dunker I. Normal wound healing of the paranasal sinuses: clinical and experimental investigations. *Eur Arch Otorhinolaryngol*. 1991;248:390–394.
20. Beule AG, Steinmeier E, Kaftan H, et al. Effects of a dexamethasone-releasing stent on osteoneogenesis in a rabbit model. *Am J Rhinol Allergy*. 2009;23:433–436.
21. Weber RK. Nasal packing and stenting. *GMS Curr Top Otorhinolaryngol Head Neck Surg*. 2009;8:Doc02.
22. Valentine R, Athanasiadis T, Moratti S, Hanton L, Robinson S, Wormald PJ. The efficacy of a novel chitosan gel on hemostasis and wound healing after endoscopic sinus surgery. *Am J Rhinol Allergy*. 2010;24:70–75.
23. Athanasiadis T, Beule AG, Robinson BH, Robinson SR, Shi Z, Wormald PJ. Effects of a novel chitosan gel on mucosal wound healing following endoscopic sinus surgery in a sheep model of chronic rhinosinusitis. *Laryngoscope*. 2008;118:1088–1094.
24. Valentine R, Athanasiadis T, Moratti S, Robinson S, Wormald PJ. The efficacy of a novel chitosan gel on hemostasis after endoscopic sinus surgery in a sheep model of chronic rhinosinusitis. *Am J Rhinol Allergy*. 2009;23:71–75.
25. Ngoc Ha T, Valentine R, Moratti S, Robinson S, Hanton L, Wormald PJ. A blinded randomized controlled trial evaluating the efficacy of chitosan gel on ostial stenosis following endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2013;3:573–580.
26. Shrime MG, Tabaee A, Hsu AK, Rickert S, Close LG. Synechia formation after endoscopic sinus surgery and middle turbinate medialization with and without FloSeal. *Am J Rhinol*. 2007;21:174–179.
27. Pomerantz J, Dutton JM. Platelet gel for endoscopic sinus surgery. *Ann Otol Rhinol Laryngol*. 2005;114:699–704.
28. Vaiman M, Eviatar E, Segal S. The use of fibrin glue as hemostatic in endonasal operations: a prospective, randomized study. *Rhinology*. 2002;40:185–188.
29. Vaiman M, Eviatar E, Segal S. Effectiveness of second-generation fibrin glue in endonasal operations. *Otolaryngol Head Neck Surg*. 2002;126:388–391.
30. Kurita K. Chitin and chitosan: functional biopolymers from marine crustaceans. *Mar Biotechnol (NY)*. 2006;8:203–226.
31. Murr AH, Smith TL, Hwang PH, et al. Safety and efficacy of a novel bioabsorbable, steroid-eluting sinus stent. *Int Forum Allergy Rhinol*. 2011;1:23–32.
32. Marple BF, Smith TL, Han JK, et al. Advance II: a prospective, randomized study assessing safety and efficacy of bioabsorbable steroid-releasing sinus implants. *Otolaryngol Head Neck Surg*. 2012;146:1004–1011.