**STUDY PROTOCOL**

**TITLE**

A single-blinded randomised trial evaluating the efficacy of chitosan-dextran (Chitodex) gel with topical steroid versus PureRegen gel on post-operative outcomes in the treatment of Chronic Rhinosinusitis (CRS)

**SHORT TITLE
Effects of Chitodex with steroid on patients having sinus surgery for chronic rhinosinusitis**

**INVESTIGATOR DETAILS AND QUALIFICATIONS**

Coordinating Principal investigator (CPI):

Name: Associate Professor Yuresh Naidoo

Qualifications/position: Associate Professor

 Otolaryngology Head and Neck Surgery

 Macquarie University Hospital, Sydney, Australia

 Ear, Nose and Throat Surgeon, Concord Repatriation General Hospital, North Shore Private, Sydney Adventist Hospital, Campbelltown Private Hospital, and Auburn Hospital.

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Roles: participant randomisation, consenting, recruitment, surgery, administering the product, safety monitoring, follow-up of participants, data collection, data entry, and data analysis.

Co-investigators:

Name:

Professor Raymond Sacks

Qualifications/position: MBBCh, FCS (SA) ORL, FRACS | Ear, Nose and Throat Surgeon​Clinical Prof. Sydney University, Professor and Chairman of Dept Otolaryngology Macquarie University

Roles: participant consenting, recruitment, surgery, administering the product, follow-up of participants, data collection, and data analysis.

Dr Arjuna Ananda

Qualifications/position: MB BS FRACS
Ear, Nose and Throat Surgeon

Roles: participant consenting, recruitment, surgery, administering the product, follow-up of participants, data collection.

**TRIAL SITES**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Site | Trial Activity | Investigators |
| Public  | Concord Repatriation General Hospital,  | consenting, recruitment, surgery, administering the product, safety monitoring, follow-up of participants, data collection,  | YN, RS, AA |
| Private | Macquarie University Private Hospital\*,North Shore Private Hospital\*,Sydney Adventist Hospital\*,Campbelltown Private Hospital\*,The ENT Centre\*. | participant randomisation,consenting, recruitment, surgery, administering the product, safety monitoring, follow-up of participants,data analysis. | YN, RS, AAYNYN, RSYN, RSYN, AA, RS |

\*An External Entity Agreement (EEA) will be completed for this site.

**PURPOSE OF STUDY (general) and AIMS (specific)**

The purpose of this study is to compare Chitosan-dextran (Chitodex) gel with topical steroid versus our current standard of care, PureRegen gel, on wound healing and post-operative outcomes in the treatment of patients with Chronic Rhinosinusitis (CRS). Chitodex and PureRegen are already known to be beneficial in controlling postoperative bleeding and promoting wound healing 1,2,7,9. We aim to compare the wound healing effects and postoperative outcomes between the two products. The ultimate goal is to optimize postoperative care which improves patient outcomes following a sinus operation for CRS.

The specific aim of this study is to compare the efficacy of a modified Chitodex gel kit with PureRegen gel (our standard of care) on wound healing and prevention of the formation of adhesions to identify if the modified Chitodex gel is superior to PureRegen gel in terms of post-operative outcomes and the reduction of oral steroid prescription. The trial will be single blinded randomised trial and will recruit patients undergoing endoscopic sinus surgery for CRS. Specific primary and secondary outcome measures will include objective and subjective symptom scores.

**OUTCOMES**

The most important clinical feature, and our primary outcome measure, is the ostial opening measurements i.e. maintenance of the drainage pathways. These measurements are taken at four time points – day 0 (operation), 2 weeks, 6 weeks, and 12 weeks post-operatively, for 3 sinus openings on each side (frontal, maxillary, and sphenoid, in mm2). This data will determine the rate of closure of these openings between treatment groups. Our hypothesis is that the Chitodex-treated sinuses will stenose significantly less (approx. 30%) than the PureRegen-treated sinuses at our clinical end-point, 12-weeks post-surgery.

Our secondary outcomes are endoscopic appearance of sinuses to assess presence of inflammation, infection and/or adhesions at other sites, which is also important and contribute to surgical success or failure. We also know that subjective symptoms should be considered as they don’t always correlate to the objective scores and can assist us in improving our patient care after surgery. Subjective symptom scores must also be considered to observe any adverse events experienced from either gel.

Objective outcomes will be assessed by a blinded investigator by way of de-identified endoscopic video recordings. The subjective symptoms scores will be reported by participants by using a self-directed symptom and comfort questionnaire specific for each side at time = 0, 2 weeks, 6 weeks & 12 weeks from the day of surgery (appendix 4).

Postoperatively, all participants will receive a empirical course of oral antibiotics and they will be instructed to perform saline douches four times daily on each side. as per routine standard of care. They will return for routine endoscopic examination and debridement of both nasal cavities at 2 weeks postoperatively and will be prescribed and instructed to perform Pulmicort steroid douches once daily for the remainder of the trial period. They will return at 6- and 12-weeks post-surgery for endoscopic examination.

The postoperative questionnaire, completed by each participant at each visit contains the subjective symptom scores, using a visual analogue scale (VAS), grading of facial pain/discomfort, bleeding, nasal obstruction, and nasal secretion for both the left and the right sides.

All endoscopic examinations will be recorded as a video for blinded grading by a different investigator for crusting, mucosal edema, infection, and granulations. Presence of adhesion will be documented regardless of size, and, additionally, a grade will be taken based on the percentage of the vertical height of the middle turbinate taken up by the adhesion. (Appendix 3 Grading proforma).

Outcome measures:
1. Ostial measurements (mm2) of frontal, maxillary and sphenoid sinuses on each side

2. Objective symptom scores on endoscopy
3. Prescribed prednisolone (oral steroids) required for sinus inflammation (left, right or both)

2. Subjective symptom scores on participant’s self-directed questionnaires.

All results will be statistically analysed at the completion of the study prior to unblinding.

**BACKGROUND AND PRELIMINARY STUDIES**

Chronic rhinosinusitis (CRS) affects approximately 15% of the general population and is characterised by sinusitis symptoms persisting for more than 3 months. Patients who do not respond adequately to oral and topical steroids, antibiotics and nasal lavage require surgical management. The surgical procedure is termed endoscopic sinus surgery (ESS) and involves removing edematous mucosa, pus and debris, as well as clearance of partitions within the sinonasal cavity to open obstructed sinuses. Stenosis of these openings (adhesion formation) is the primary cause of failure of this operation and results in revision surgery being required.

The aim of surgery itself is trifold:

1. to improve aeration of the sinuses to enable drainage of mucus out of the ostial openings
2. to recreate a normal homeostatic environment and,
3. to optimise the sinuses for the application of topical products during the postoperative period. The topical products are designed to combat persistent infection, inflammation and polyp (re)formation.

Recalcitrant CRS is defined as CRS which is persistent despite surgical management. Much research is currently underway to differentiate this group of patients from those who are responsive to medical and surgical management, to characterise the factors contributing to recalcitrance, and to develop strategies to improve symptoms in these patients.

Previous studies:

Nasal dressings are commonly used following endoscopic sinus surgery in an attempt to prevent ongoing bleeding and to improve the wound healing process. There is still little agreement between surgeons on the optimal choice of nasal dressings following endoscopic sinus surgery, or whether nasal dressings are required at all 1a.

A 2012 study has shown that Chitodex gel (in its original form without additional components) is beneficial to wound healing 3 months following sinus surgery. Patients used as their own controls showed great improvement in healing in terms of ostial areas (ostia = opening to sinuses). In the frontal sinuses, the sides that received Chitodex gel, maintained an average of 66% of their original ostial size, compared to 32% in the control (no test substance) sides. Similarly, the sphenoid sinuses showed an average of 85% diameter preservation on the Chitodex gel side, compared with 47% in the control sides. The third set of sinuses, the maxillary sinuses, showed 74% original diameter preservation in the Chitodex gel sides compared to 54% in the control sides1.

A follow-up trial was performed where Chitodex gel was combined with a topical steroid solution (budesonide, Pulmicort®) or applied without steroid (CD-gel control) and applied in a similar manner following sinus surgery for similar patients (Ooi M et al, data analysis in progress2). Preliminary results of that study have shown reduced inflammation during the early postoperative period (compared to control) and even further improvements in ostial stenosis at 3 and 12 months.

Chitodex is a combination of Chitosan, which is a natural polymer obtained from chitin found in shellfish and squid that can be used as a carrier agent for other agents such as steroids or antibiotics, and dextran derivatives. Chitosan is used as a preservative to foods, an antimicrobial coating on fruits and vegetables for human consumption, a coating for seeds before planting, and a hydrating cosmetic product as well as an additive to shampoos and toothpaste3. It has recently been studied as an antiadhesion material in a number of animal and human abdominal and pelvic studies and has shown antiadhesion properties4,5. A research team developed a chitosan-dextran derivative gel (Department of Chemistry, University of Otago, Dunedin, New Zealand) formed by cross linking chitosan and dextran derivatives which fragments and dissolves over a period of 7-9 days6. In this study, as with the previous human trials 2, 2b, Chitodex gel is going to serve as a carrier for a topical steroid.

Triamcinolone-impregnated nasal dressing has been shown to significantly improve sinus mucosal healing after ESS, when compared to no dressing2c.

Triamcinolone 40mg/1ml is going to be added to the gel in the form of a solution and it is going to be used only in the Chitodex side. We have chosen this steroid because this steroid solution is always available in ENT operating theatres, while budesonide is prescription only available in the form of Pulmicort ™. Triamcinolone is injected if indicated (significant mucosal oedema i.e. polyps) during sinus procedures and for other ENT procedures, such as vocal cords to reduce irritation/inflammation. It is used in the sinuses under the discretion of the ENT surgeon injected into the inferior turbinates or nasal polyps as part of routine ENT patient care. Triamcinolone 40mg/ml is listed under the MIMS for hayfever, asthma and intra-articular injections and is used regularly and routinely in the upper airway. The Investigators will advise theatre coordinator prior to surgery list, when an ampoule of Triamcinolone is required for research purposes. The hospital will then invoice the surgeon for the cost of it.

Chitodex sinus gel kits will be provided *pro bono* by Professor Wormald at the Otolaryngology, Head and Neck department of The University of Adelaide because he uses this kits as his standard of care and has conducted previous clinical trials using this gel 1, 2, 2b

PureRegen Gel Sinus (BioRegen Biomedical, Changzhou, China) is the current standard of care used by the Investigators in this study. It is a 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. The effects of PureRegen Gel on optimizing post-operative wound healing and synechiae prevention in sinus cavity have been reported in previous studies7-9. The use of PureRegen demonstrated less fibrosis and synechia formation in the frontal recess and ostium7. In a study comparing PureRegen Gel Sinus with Merocel, the former revealed faster reepithelization at 2-week follow-up (9.3% v 1.9%, p=<0.01) and less scar tissue formation at 12-week follow-up (0% v 7.41%, p= <0.01)9. A randomized controlled trial by Matheny et al. showed that PureRegen Gel Sinus improved the overall total endoscopic grading score at both 6 and 12 weeks (2.34 v 2.79, p=<0.05 and 2.10 v 2.45, p =<0.05, respectively)8.

PureRegen gel cannot be modified to carry drugs. Chitdex gel can be easily modified to include a small amount of topical steroid which may reduce the need for prescription oral steroids. Oral steroids are prescribed to reduce inflammation and this depends on the levels of inflammation of sinuses or the presence of polyps. Knowing the benefits of both Chitodex gel and PureRegen gel on wound healing and post-operative outcomes, we now propose a study to compare both products in postoperative care of sinus surgery for CRS. These devices are absorbable and last 10-21 days in the sinus cavities6.

**PARTICIPANTS**

Selection/ inclusion criteria:

Participants who meet ALL of the following criteria will be offered inclusion in the study:

1. Those who have had symptoms of chronic rhinosinusitis (nasal discharge, postnasal drip, nasal obstruction, facial pain and pressure, lack of sense of smell) that has been previously persistent for greater than 3 months AND
2. are over 18 years of age AND
3. are able to give written informed consent AND
4. are indicated to undergo endoscopic sinus surgery and willing
5. can commit to return to the clinic for 2-, 6- & 12-weeks post-operative endoscopic examination (as per standard of care).

Exclusion criteria:

1. allergy to shellfish
2. pregnant or breastfeeding
3. hepatitis or blood disorders.
4. allergy to steroids
5. Covid-19 positive

Withdrawal criteria:

1. participant who do not return for the second part of this study
2. participant who exhibit an allergic reaction to any test substance (including antibiotic)
3. any participant who requests withdrawal from the study. No reason will be required.
4. Patients tested positive for COVID within 12 weeks post-surgery.

**STUDY PLAN AND DESIGN**

The aim of this study is to compare the effectiveness of wound healing between modified Chitodex gel and PureRegen gel to optimize the postoperative results of patients with chronic rinosinusitis undergoing endoscopic sinus surgery (ESS). The importance of optimizing the healing results is to maximize the delivery of topical treatment after surgery to a wide opened sinus cavity and reduce the need for oral steroids. Both Chitodex gel and PureRegen gel have already been studied and demonstrate effecacy in wound healing but there is no study comparing these two products.

Participants who meet ALL of the inclusion/exclusion criteria as outlined in the previous section will be offered participation in this study.

**Recruitment**

Investigators will recruit participants from their own patients. Participants will be recruited from The ENT Centre, a tertiary private practice (private patients) or in the ENT clinic of the public hospital site (Concord), by the Investigators. If they meet the inclusion and exclusion criteria, they will be offered inclusion in the study and will have every right to accept or decline the offer to participate. Acceptance or non-acceptance of offer will not affect any other aspect of their surgical/hospital care or their position on the surgical waiting list. The Investigator will explain all of the details of the study including purposes, procedures and risks of the research. A Participant Information Sheet will be provided to the participants. If participants do not understand English, a health care interpreter will be organized to translate the consent document in a language that they understand. Participants will have an opportunity to ask questions. Participants will be free to agree to participate in this research project as described and free to withdraw at any time during the study without affecting their future health care.Following acceptance, the participants will be asked to give informed written consent. Participants will have up to the time of their surgery to reconsider their participation. If patients opt not to participate in this study their treatment will follow as the recommended treatment for a patient with CRS which includes ESS.

Participants will remain under the care of the same Investigator/ENT surgeon for the duration of the trial. They will be listed at the appropriate hospital (public or private) as per standard of care.

**Sinus Surgery and Administration of the Treatment Gels (unblinded)**

At the hospital where the ESS is scheduled (see Trial Sites), the surgeon/investigator will perform the schedule ESS, record the endoscopic procedure, use a 5mm ball probe to insert into each sinus, left and right, ostial openings; frontal, maxillary, and sphenoid (this visual will be used later when calculating the baseline ostial measurements) and apply the study gels. The participants will have been randomised to receive Chitodex gel with triamcinolone and PureRegen gel alone on either sinus cavity immediately upon completion of ESS.

|  |
| --- |
| **Treatment sides** |
| **Chitodex + Triamcinolone gel** | **PureRegen gel** |
| Chitodex 10 ml inc triamcinolone 1ml | PureRegen 10 ml  |
| Oral antibiotics for 10 days | Oral antibiotics for 10 days |
| Saline irrigation 4 times per day | Saline irrigation 4 times per day |
| Pulmicort irrigation once daily To start 2 weeks post-surgery | Pulmicort irrigation once daily To start 2 weeks post-surgery |
| Follow-up at 2-, 6- and 12-weeks for naso-endoscopy | Follow-up at 2-, 6- and 12-weeks for naso-endoscopy |

At the end of the ESS, before being woken from general anaesthesia, each participant will receive 10 ml of PureRegen gel into one side and 10 ml of Chitodex into the contralateral side as a one-off treatment. The gels will be placed into the newly opened sinus ostiums and cover the sites of incised mucosa. The airway is maintained (i.e. patients will still be able to breathe through their nose after surgery). These devices are absorbable and last 10-21 days in the sinus cavities6. Due to the slight colour difference of the gels, Chitdex has a yellow/orange colour and PureRegen is clear, the administering clinician will not be blinded to the treatment groups/sides at this stage.

Post-operative care will proceed for all patients included in this study as per standard protocol for ESS surgery which include 10 days of post-operative antibiotics, nasal irrigation with saline and steroid wash (Pulmicort ®) after 2 weeks (first postoperative visit). The prescription for these medications will be provided by the investigators but the cost will be covered by the patient, as per standard of care.

**Post-Surgery Follow-Up Visits (unblinded)**

The participant will either to return to The ENT Centre (all private patients) or Concord Hospital ENT clinic (public patients) to see their ENT surgeon/Investigator at 2 weeks post-surgery for a review and cleaning of their sinuses, as per standard of care. The gels will likely be absorbed by this point, therefor the surgeon may be blinded to the treatment groups/sides. A recording of their endoscopic sinus examination will be made using the endoscopic camera equipment, the surgeon/Investigator will again use a 5mm ball probe to insert into each sinus, left and right, ostial openings; frontal, maxillary, and sphenoid (this visual will be used later when calculating the ostial measurements). The participant will be asked to complete a subjection symptom score sheet (Appendix 4).

The participant will return the same clinic for the 6-week and 12-week post-surgery visits. An endoscopic recording of the examination will be made in the same manner, and the participant will be asked to complete the same subjective symptom score sheet. See Table below.

| **Visit** | **Standard of Care Procedures** | **Study-Related Procedures** |
| --- | --- | --- |
| 0. Recruitment into the study |  | Symptom questionnaire |
| 1. Sinus surgery | Endoscopic sinus surgery  | Endoscopic video recording |
| Application of PureRegen gel to the sinuses; left and right | Application of Chitodex steroid gel to one side (left and right sides of your sinuses are randomly selected by a computer to receive one of each type of gel) |
| Oral antibiotics – 10 days, and |  |
| Saline nasal flushing – 4 times per day for 2 weeks |  |
| 2. 2 weeks post-surgery follow-up visit 1 | Return to clinicEndoscopic examination and clean | Endoscopic video recordingSymptom questionnaire |
| Pulmicort® nasal flushing – 1 times per day |  |
| 3. 6 weeks post-surgery follow-up visit 2 | Return to clinic Endoscopic examination | Endoscopic video recordingSymptom questionnaire |
| 4. 12 weeks post-surgery follow-up visit 3 | Return to clinicEndoscopic examination | Endoscopic video recordingSymptom questionnaire |

**Grading of Endoscopic Video Recordings (blinded)**

The endoscopic video examination videos from each surgeon/investigator will be de-identified and scored by one of the other Investigators for ostial measurements (using the ball probe for scale) and grading of infection (pus), edema, granulation tissue, and crusting using a standardized non-validated ordinal scale for both sides [Appendix 3].

**De-Identifying and Randomization:**Once the participant has been recruited to the trial, the CPI will enter them into SLHD REDCap software and allocate them a Record ID (Trial ID) and this ID will be used on all data collection (symptom questionnaires, grading proformas, endoscopic examination video recordings). The REDCap record will also be used to store their randomised arm; whether their left and right sinuses to receive standard of care PureRegen gel and Chitodex gel to the other side. Using a within-subject design, included patients will receive Chitodex on one side of the sinus cavity and PureRegen Gel on the contralateral side. Randomised will be performed by the CPI. Recruited participants will be entered sequentially into the REDCap project. GraphPad Quickcalcs software (<http://www.graphpad.com/quickcalcs/index.cfm>) will be used to randomise the sides receiving which gel. Using the above link, select Random Numbers> Randomly Assign Subjects to Groups> Randomly choose a group for each subject. Assign 50 subjects of 2 groups. Repeat 1 times. This will produce a randomly ordered list assigning each recruited participant (starting with ID 1) to a group, either A or B. Group A being PureRegen gel applied to the left sinus and Chitodex steroid gel to the right sinus. Group B being Chitodex steroid gel to the left sinus and PureRegen gel to the right sinus. The PI will advise the surgeon (administrator of the gel) which side to apply which product. The endoscopic recording can be used to verify this was performed correctly as the gels each have a different colour.

**Statistical power calculation:**

An a prior power calculation was run to determine the minimum sample size for the statistical analysis. The sample size calculation assumes a 95% level of confidence, a desired power level of 0.80, and a small effect size between treatment groups in each sinus type (Cohen's d=0.3).

Using these assumptions, the sample size required for this analysis was estimated to be 25. Assuming a dropout rate of 20% (and assuming that a patient dropping out at any point of the study will lead to the removal of all their measurements from the study), this gives a desired recruitment number of 31.

**Analysis:**

The ostial measurements will be compared between Chitodex and PureRegen treatment type at 3 repeated time points after the intraoperative measurements (at 2,6 and 12 weeks), both as raw measurements and as a proportion of the baseline intraoperative measurements. These measurements will also be stratified into the 3 different sinus types (Frontal, Sphenoid and Maxillary).

These measurements will be summarised as means with standard deviations as appropriate. The descriptive statistics will be reported with stratification by treatment type.

The superiority analysis to be conducted will be a Repeat Measured ANOVA (RM-ANOVA), where 2 treatment groups (Chitodex and PureRegen) are compared against 3 sinus positions and 4 repeated time measurements. The independent categorical variables will be 'treatment type', 'sinus type' and 'time', with the dependent variable being the ostial measurement. Interaction effects between treatment type, sinus type and time will be investigated for significance in the RM-ANOVA model.

The model will be controlled for the variance contributed by the differences in each patient (i.e. there are 24 ostial measurements for each patient across the 4 times), because some amount of the variance in measurements will be explained by the difference in healing within the patients themselves.

Post-hoc adjusted student t-tests will compare the mean difference between the treatments for each sinus type at each time measurement, at the 0.05 significance level. The standard error of these t-tests will also be adjusted for paired samples, as the independence of observations does not hold (there are two observations per person at each time for each sinus position that are being tested). All t-tests will be 2-tailed.

COVID-19 protocol deviation plan:

This clinical trial would proceed as per the protocol while elective ENT ESS surgeries are permitted to be performed during the COVID-19 pandemic by NSW Health. If restrictions were to be implemented on these surgeries, we would be unable to recruit any new participants to this trial and it would resume at a later date. Participants already on the trial would continue to be followed-up as per standard of care. As the endoscopic examinations must be face-to-face, if restrictions prohibit these visits, the trial would be placed on hold. The participants would be excluded from the trial and followed-up by telephone until 12-weeks post-surgery, and then face-to-face at the first available opportunity. Existing participants will be provided with contact phone numbers to report any adverse events (blurred vision, sudden fever, vomting, dizziness, diarrhea, or rash), or may present to a hospital emergency department for assessment.

**Reporting:**

Protocol deviations, breaches and/or amendments, safety reporting and annual reports will be submitted/reported as per Concord Hospital Research Office Post Ethics Approval process - <https://www.slhd.nsw.gov.au/concord/Ethics/post_approval.html>

**Drugs to be used:**

|  |  |
| --- | --- |
| **Chitodex gel including topical steroid** | **PureRegen gel** |
| Chitogel kit (see product brochure) will be supplied by Chitogel Ltd, Dunedin, NZ. Sterile surgical kit contains chitosan, dextran-aldehyde, and buffer solution. Components mixed with syringe included to form a gel. See Chitogel Technique Guide for FESS. Volume applied 10mL.Triamcinolone 40mg/1ml injectable. Solution will be substituted for 1ml of the buffer solution in Chitogel kit. Steroid contained within the formed gel. This solution is readily commonly used for the management of upper airway inflammation and is in routine use by ENT surgeons in Australia. The solution is available in ENT operating theatre as standard practice. | PureRegen gel: (see product brochure) hyaluronic acid gel comes ready-made in sterile syringe. 10mL. Volume applied as per Chitogel Technique Guide for FESS. |

**ETHICAL CONSIDERATIONS**

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There have been no adverse events reported in previous clinical trials using Chitodex gel1, 2, 2b or triamcinolone-impregnated post-ESS nasal dressing2c.

The potential risks of this study are:

1. Allergic reaction to any of the test substances – Chitodex gel, shellfish, topical steroids, and PureRegen gel sinus. If the allergic reaction is mild, this should pose minimal discomfort to the participants and is easily managed by short-term medicines such as antihistamines and cessation of product (gels removal by suction). If the allergic reaction is moderate, this could cause much more discomfort to the patient, but again is manageable by medical means. However, if the allergic reaction is severe, this could be life-threatening. There have been NO previous allergic reactions to any of the test substances in previous studies. Participants with known or suspected allergies to shellfish or steroids will be excluded from the trial.
2. Some patients might experience discomfort or a sense of nasal obstruction with the gel *in situ*. We expect that this sensation would be transient and resolve as the gel resorbs/washes out/blown out. There have been mixed reports of participants discomfort following both application of the gel as well as control (no substance applied) in previous studies therefore discomfort due to the gel has not been a consistent report.
3. There have not been any reports of pain from participants who have had the gel applied in previous studies.
4. Chitodex and PureRegen gel kits will not be used in surgery involving any of the following complications: cerebrospinal fluid leak, any form of ophthalmic complication, including but not limited to orbital haemorrhage or hematoma and exposure of the orbital tissues; recruited participants with these complications will be excluded from the study.

 Risks related to the ESS surgery will be explained as part of surgical consent process. All patients undergoing ESS surgery are given the Royal Australasian College of Surgeons Functional Endoscopic Sinus Surgery Patient Guide which includes the risks and complication related to the surgery (Appendix 5).

**SPECIFIC SAFETY CONSIDERATIONS (e.g. Radiation, toxicity)**

No radiation will be used in this study.

Toxicity is very unlikely in this study.

Chitodex gel has an excellent safety and efficacy profile, is already used to improve wound healing after endoscopic sinus surgery1 and has been approved by FDA as a medical device type III for use after sinus surgery (currently under review by the TGA). PureRegen gel also has an excellent safety and efficacy profile, and it has demonstrated improvement in endoscopic sinus sugery outcomes7-9.

Short-term use of topical corticosteroid sprays and irrigations have been shown to have no impact on the hypophyseal–pituitary–adrenal axis in adults which is in agreement with rapid hepatic metabolism of these intranasal corticosteroids10,11. Topical corticosteroids are best delivered via a high-volume, high-pressure delivery device in the postoperative setting12. Yet, only 5% of a topical corticosteroid solution, or 50ug, is retained in the postoperative sinuses when applied via a squeeze bottle, minimizing side effects13. A study that used positron emission tomography to monitor intranasal administration of Tramcinolone acetonide aqueous nasal spray demonstrated clearance of drug from the frontal cavity toward the throat (with a maximum of 8% of the dose in the sinuses at any one time)14.

**DRUGS/DEVICES**

For all approved clinical trials, it is a HREC condition that it is registered in a publicly accessible trials registry prior to enrolment of the first participant. This is the responsibility of the investigator; hence we have applied for clinical Trial notification under TGA for the use of Chitodex gel (not TGA-approved) and Triamcinolone injectable (ARTG Entry 264407) as a topical steroid incorporated into the gel. A CTN will be submitted to the TGA to use both Chitodex gel and triamcinolone for topical (off-label use).

This clinical trial will also be registered to the public on the Australian New Zealand Clinical Trials Registry (ANZCTR).

This study includes the use of two nasal dressing, which are categorised as ‘medical devices’. PureRegen gel is the current standard of care in this patient population for the Investigators in this trial. Chitodex is not a standard of care nasal dressing used by the Investigators in this study but is commonly used by the Otolaryngology, Head and Neck Surgery department of The University of Adelaide who will provide Chitodex kits at no charge. Chitodex gel sinus surgery kits are approved by the FDA and under review with the TGA. .

**ANALYSIS AND REPORTING OF RESULTS**

Data will be collected by one of the study investigators following each clinic session and stored in a locked office in the ENT Centre. Only the Investigators in the study (and supporting staff) will have access to the data. The data will be analysed and recorded electronically on a computer by the Investigators(s). All data will remain the property of The ENT Centre and be kept indefinitely unless a participant requests the permanent deletion of their research-related data (e.g. if they wish to withdraw from the study).

There will be no access to participant’s electronic medical records at any of the hospitals listed under Trial Sites section.

**OTHER RELEVANT INFORMATION (e.g. Advertising, publishing)**

There will be no advertising associated with this study.

Will be registered with ANZCTR.

**OTHER ETHICS COMMITTEES TO WHICH THE PROTOCOL HAS BEEN SUBMITTED**

**GOVERNANCE**

Monitoring

The Sponsor (i.e. the Investigators) are responsible for the on-going safety evaluation of the investigational products and devices. Investigators will record and report any adverse event to the CPI, HREC and TGA in accordance with NHMRC (Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods 2016). Safety report will be submitted to HREC annually.

Complaints
A participant may make a complaint directly to the CPI of this study. Otherwise, any concern or complaint from a participant or any other person about the conduct of a project should be directed to the attention of the HREC Executive Officer, or their delegate, who will notify the Chairperson as soon as possible (SLHD HREC SOP 020 2017).

**DATE OF PROPOSED COMMENCEMENT AND DURATION.**

Proposed commencement: immediately following ethics approval.

Duration until last participant completes follow-up will be approximately 6 months.

**CONFLICTS OF INTEREST**

Professor Wormald at The Department of Otolarngology, Head and Neck Surgery, The University of Adelaide is a shareholder of Chitogel Ltd and he will be supplying the Chitodex kits used in this study free of charge (pro bono). He is not an Investigator and will not be involved in study-related activities. Investigators may consut with him during preparation of the manuscript but no data will be shared. Otherwise, he will have access to the published paper.

**SIGNATURES OF INVESTIGATORS**

The Coordinating Principal Investigator to confirm that the protocol has been read and endorsed.

The signatures may be in a covering letter or at the end of the Protocol.

**APPENDICES**

**Appendix 1** - Protocol flow chart

Coordinating Principal investigator: Associate Professor Yuresh Naidoo

| Milestone | Time period |
| --- | --- |
| HREC approval | February 2021 |
| Governance and site approvals | March 2021 |
| TGA CTN approval | March 2021 |
| Clinical Trial | March 2021 – September 2021 |
| Data analysis | October 2021 – November 2021 |
| Submission for Publication | December 2021 |

**Appendix 2**: Patient recruitment Checklist

(to be completed by surgeon at Time = 0)

Patient Name: Date:

Clinician Name:

**Inclusion criteria (Need to answer YES to all of these)**

|  |  |  |
| --- | --- | --- |
| Is the patient over 18 and able to give competent informed consent? | Yes  | No  |
| Is the patient willing to return to the clinic at 2 weeks, 6 weeks and 12 weeks after recruitment? | Yes  | No  |
| Does the patient have symptoms of CRS? | Yes  | No  |
| Does the patient have symptoms of active infection? | Yes  | No  |
| Does the patient have signs of CRS? | Yes  | No  |
| Does the patient have signs of active infection? | Yes  | No  |
| Has the patient failed oral antibiotics therapy at least once prior to their recruitment to the study? | Yes  | No  |

**Exclusion criteria (Need to answer NO to all of these)**

1. allergy to shellfish
2. pregnant or breastfeeding
3. Hepatitis or blood disorders.
4. allergy to steroids
5. Covid-19 positive

**Appendix 3:** Grading Pro-forma – to be completed by surgeon

Patient Name:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Time of assessment: 0 week (at recruitment)/2 week/6 weeks / 12 weeks

|  |  |  |
| --- | --- | --- |
|  | **L** | **R** |
| **ADHESIONS** |
| % Middle Turbinate taken up by adhesion | 0, 1-25, 26-50, >50% | 0, 1-25, 26-50, >50% |
| Adhesions Divided | Yes/No | Yes/No |
| **MUCUPURULENT DISCHARGE**  |
| Ordinal Scale (0-2) | No visible evidence of infection | 0 | No visible evidence of infection | 0 |
| Mild mucopurulent drainage | 1 | Mild mucopurulent drainage | 1 |
| Gross mucopurulent drainage with obvious frank infection | 2 | Gross mucopurulent drainage with obvious frank infection | 2 |
| **MUCOSAL OEDEMA** |
| Ordinal scale (0-3) | No visible mucosal oedema | 0 | No visible mucosal oedema | 0 |
| Mild mucosal oedema without obliteration of the ethmoid cavity | 1 | Mild mucosal oedema without obliteration of the ethmoid cavity | 1 |
| Severe mucosal oedema obliterating most of the ethmoid cavity | 2 | Severe mucosal oedema obliterating most of the ethmoid cavity | 2 |
| Frank polyposis | 3 | Frank polyposis | 3 |
| **CRUSTING** |
| Ordinal Scale (0-2) | Absent | 0 | Absent | 0 |
| Mild | 1 | Mild | 1 |
| Severe | 2 | Severe | 2 |
| Debridement | Yes/No | Yes/No |
| **GRANULATIONS** |
| Ordinal Scale(0-3) | No visible granulations | 0 | No visible granulations | 0 |
| Mild | 1 | Mild | 1 |
| Moderate | 2 | Moderate | 2 |
| Severe | 3 | Severe | 3 |
| **OSTIAL MEASUREMENTS (mm2)** | **R** |  | **L** |  |
| Frontal |  |  |  |  |
| Maxillary |  |  |  |  |
| Ethmoid |  |  |  |  |
| Sphenoid |  |  |  |  |

**Prednisolone prescribed? Y/N
If yes, for which side is it indicated? L / R / Both**

**Appendix 4** : Symptom questionnaire

The ENT Centre

SELF-DIRECTED SYMPTOM AND COMFORT form

**Title:** A single-blinded randomised trial evaluating the efficacy of chitosan-dextran (Chitodex) gel with topical steroid versus PureRegen gel on post-operative outcomes in the treatment of Chronic Rhinosinusitis (CRS)

**Protocol Number**: Version 4.0 October 2020

Dear Participant,

Thank you for your participation in this study.

The following evaluation form should only take you **less than 5 minutes** to complete.

The purpose of this evaluation form is to assess symptom outcomes from your point of view as the patient, which is an important consideration in the outcomes of this study.

On the page attached, please indicate your assessment of the following factors on the scale provided (0-10)

Yours sincerely,

Assistant Researcher

Trial Participant ID: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Today’s Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_

Time of assessment: Surgery date, Time = 0 weeks

2 weeks / 6 weeks / 12 weeks since surgery

Explanations of scale:

**Facial Pain/Discomfort**: 0 is no pain or discomfort, 10 is the worst pain you have ever experienced

**Bleeding**: 0 is no bleeding, 10 is bleeding requiring re-operation to control it

**Nasal Obstruction**: 0 is a perfect airway which is very easy to breathe through, 10 is completely blocked with no air movement through that side.

**Nasal Secretion/throat drip**: 0 is no nasal secretions, 10 is copious secretions with constant nasal dripping.

**Throat drip**: 0 is no nasal secretions, 10 is copious secretions with constant nasal dripping.

**Sense of smell**: 0 is no smell ability at all, 10 is best smell ability.

e.g. Moderate pain 

Please evaluate left and right sides separately

|  |  |
| --- | --- |
| **Q 1** | **Pain/Discomfort Score** |
|  | **Left** | **Right** |
| **Facial pain/ discomfort** | image.png | image.png |
| **Bleeding – Nose and Throat** | image.png | image.png |
| **Nasal Obstruction/ Breathing** | image.png | image.png |
| **Nasal secretions** | image.png | image.png |
| **Drip at back of throat** | image.png | image.png |
| **Sense of smell** | image.png | image.png |

**Appendix 5 :** Patient Guide to ESS





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