Perioperative Oral Steroids for Chronic Rhinosinusitis Without Polyps

NCT02748070

February 17, 2015

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1. PURPOSE OF THE STUDY

a. Brief Summary

After patients with chronic rhinosinusitis (CRS) undergo sinus surgery, they are typically instructed to take oral steroids for several days to weeks. However, there is limited data to suggest this is a beneficial practice, and oral steroids have been shown to have significant and unpleasant side effects. This study will investigate whether there is truly evidence based utility to the use of steroids after sinus surgery

b. Objectives

Chronic rhinosinusitis is a disease that affects an estimated 13% of the adult population. Patients with this disease suffer from reduced quality of life, impaired sleep, fatigue, acute infections, and chronic pain. Healthcare expenditures for CRS are estimated at $8.6 billion annually, with the majority of costs arising from repetitive physician visits, emergency department encounters, and medications. Despite its prevalence, relatively little is understood about optimal medical therapy in the post-operative period. As described above, oral steroids are routinely prescribed after sinus surgery based on anecdotal data and expert opinion rather than convincing, randomized controlled data. The aim of conducting this study, therefore, is to to determine if oral steroids have a role in the peri-operative treatment of patients with CRS. This study would contribute a wealth of important data to the field of Rhinology and the management of CRS. The role of steroids in the peri-operative period would be further elucidated, providing randomized controlled data with which providers may make informed therapeutic decisions. In summary, the results of this study have significant potential to influence current practice and management guidelines.

c. Rationale for Research in Humans

The purpose of the study is to test the efficacy of of a medication in individuals with CRS, which is not a disease known to be accurately duplicated in any other model.

2. STUDY PROCEDURES

a. Procedures

Screening: Patients who have been recommended to undergo endoscopic sinus surgery by our department will be recruited for the study and informed of its purpose pre-operatively. SNOT22 scores (a quality of life survey well established in Rhinology) and Lund-Kennedy endoscopic exam scores (an quantitative clinical assessment of disease severity) will be recorded in their medical records. This is the same protocol performed for all patients seen in our clinic regardless of their enrollment in the study. Randomization and Treatment Groups: The patients that wish to participate will be randomized into two treatment arms by our nurse practitioner based on a random number generator. They will receive one of the following post-operative regimens: 1) oral steroid (treatment) + steroid spray (treatment) 2) oral placebo (control) + steroid spray (treatment) These medications will be manufactured and packaged by an independent compounding pharmacy, and prescribed by our nurse practitioner at the preoperative visit. Patients will begin their therapy on the first post-operative day. All oral steroid regimens will be given in our institution's standard 12 days taper, while topical steroids will be delivered via a metered dose nasal spray bottle for two weeks. All study patients will receive identical perioperative antibiotic therapy. We do not anticipate these medications to be an inconvenience to study patients as all proposed interventions are not different from routine post-operative care. In addition, patients undergoing surgery will have already trialed these medications as part of their pre-operative medical therapy. Surgery: Routine endoscopic sinus surgery will be performed per our institution's standard protocol. In this step there will be no difference in treatment from those patients not enrolled in the study. Post-Operative Care: At this point, patients will begin therapies according to the treatment arm to which they have been randomized. Study patients will attend post-operative appointments at identical time points to non-study patients. These will take place at the following intervals: Post-operative visit 1: 1-2 weeks Post-operative visit 2: 6-8 weeks Post-operative visit 3: 12-16 weeks Post-operative visit 4: 6 months Experimental therapy will finish after 2 weeks. At this visit, all patients will then be maintained on intranasal steroid spray and nasal saline irrigations, which is the commonly employed therapeutic standard. Thereafter, patients will, per standard protocol, be followed on an observational basis depending on the severity of symptoms and response to treatment. At each visit, as is done for all individuals, SNOT-22 and LundKennedy endoscopic exam scores will be repeated and recorded.

b. Procedure Risks

This study does not seek to evaluate a novel research procedure. Rather, we endeavor to determine if a procedure already in place nearly universally is, in fact, beneficial, as there is a

distinct lack of evidence of suggest so. Overall, we are investigating a procedural method that will have fewer side effects than the currently accepted practice.

c. Use of Deception in the Study

NA

d. Use of Audio and Video Recordings

NA

e. Alternative Procedures or Courses of Treatment

All reasonable alternatives are included as a treatment arm in this study. There is no standard of care that is being withheld from patients in any group.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes, patients will stop all experimental therapies at the 2 week mark. They will then be placed on the typical post-operative regimen, which includes a nasal steroid spray and twice daily saline irrigations. They will continue to be followed in our clinic after the 4 week mark, and their therapies tailored to their current symptoms and the endoscopic appearance of the nasal cavity.

g. Study Endpoint(s)

Currently, our post-operative protocol dictates that patients will be seen in clinic at 1 week, 3 weeks, and 6 weeks after surgery. We will only slightly alter this timeline for study patients. At the 2 week appointment, all experimental therapies will be completed. Patients will then be started on intranasal steroid sprays and saline irrigations so as not to deviate for an extended period from currently accepted practices. We will use the final scheduled appointment at 4 weeks after surgery as the official end point for comparison of treatment arms. Additionally, outcomes evaluated will be the symptom questionnaire and the endoscopic exam score at each visit. If, during the course of follow up, one regimen proves to be clearly superior to another, the study will be terminated and patients will receive the optimal therapy. By power analysis, we require 50 patients to achieve statistical significance. If there is a clearly optimal therapy determined in these first 50 patients, we will end our research at that time. All patients will continue to be followed beyond 4 weeks depending on symptom severity and response to treatment

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Currently, the preferred treatment regimen for patients with chronic rhinosinusitis (CRS) with and without polyps after endoscopic sinus surgery involves a nonstandardized combination of oral steroids and antibiotics. The European Position Paper on Rhinosinusitis and Nasal Polyps offers guidelines for surgeons in the appropriate therapies to improve patient symptoms based on data available in the literature to date. The use of oral steroids in CRS is associated with level IV evidence and a category C recommendation, indicating a lack of randomized controlled data to

support its use (1). Therefore, this almost universal current practice is perpetuated by anecdotal data and expert opinion. Furthermore, systemic steroids are associated with known significant side effects and potential drug interactions. These may be severe and include but are not limited to high blood pressure, hyperglycemia and diabetes, adrenal suppression, weight gain, glaucoma, osteoporosis, fluid retention, gastrointestinal bleeding, ulcers, and mood changes (2). Thus, oral steroids potentially pose a significant risk, have unproven benefit, and are not appropriate for repeated or longterm use – an unfortunate obstacle in treating a chronic disease. Recently, steroids dissolved in a saline irrigant have been increasingly used and proven to be effective in the routine management of CRS. Furthermore, several studies have suggested the utility and safe side effect profile of these medications; however, the data supporting their use as a perioperative treatment is distinctly lacking. While the data to support the utility of topical steroids in the treatment of CRS is evident, relatively few groups have explored topical steroid irrigations specifically as a peri-operative intervention. Fandino et al conducted a meta-analysis of 13 randomized clinical trails and cohort studies examining the use of topical steroids delivered via drops, sprays, nebulizers, or irrigations for patients with CRS with nasal poylps who had previously undergone endoscopic sinus surgery. According to his analysis, intra-nasal corticosteroids had a significant beneficial effect on symptom scores and a reduction in polyp scores. Additionally, the use of INCS decreased the rate of polyp recurrence, and did not alter adrenocorticotropic hormones post-intervention, suggesting the intra-nasal delivery method to carry less risk than the oral version (3). Snidvongs et al conducted a study with 111 patients and reported significant improvement in symptom scores and endoscopy scores over those who did not receive postoperative topical steroids (4). Jang et al retrospectively evaluated 60 patients postsurgically who were treated with topical steroid deliveries and showed a significant decrease in quality of life and endoscopy scores after patients stopped their treatments (5). In summary, the data supporting the use of steroids in patients with CRS immediately after endoscopic sinus surgery is sparse. We, therefore, seek to more definitively elucidate the role and utility of steroid treatment in the peri-operative period. Furthermore, per our review of the literature, there has been no direct comparison of the traditional oral regimen to topical therapy (nasal spray). Could these be proven equally effective, topically delivered steroids may be considered as a replacement for systemic steroids. This would represent a significant shift and improvement in the current post-operative management of CRS. Patients would avoid the innumerable side effects of oral steroids, which are detailed above. Furthermore, while oral steroid usage is often limited by unwanted side effects, a topical regimen may be sustained over a prolonged period as a maintenance therapy if symptoms necessitate.

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b. Findings from Past Animal Experiments

None

4. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	Prednisone
Dosage:	10-40mg daily
Administration Route	Oral
New and different use? (Y/N)	N
Commercial Product 2	
Name:	Flonase
Dosage:	50ug/spray
Administration Route	Nasal
New and different use? (Y/N)	N
Commercial Product 3	
Name:	NA
Dosage:	NA
Administration Route	NA
New and different use? (Y/N)	NA

5. PARTICIPANT POPULATION

a. Planned Enrollment

Based on a current rate of 12-15 endoscopic sinus surgeries weekly, as well as allowing for a significant percentage of patients who do not desire to participate in the study, we anticipate between 80 and 100 patients to enroll. The study will be conducted only at Stanford Hospitals and Clinics. Participants will be those with CRS with and without polyps who have been recommended and consented for endoscopic sinus surgery. These participants will be used because they suffer from the specific disease for which we endeavor to research alternative therapies

b. Age, Gender, and Ethnic Background

We will recruit patients >18 that are able to provide consent. There will be no gender or ethnic exclusions.

c. Vulnerable Populations

NA

d. Rationale for Exclusion of Certain Populations

Children will not be included in this study as it is not typical for endoscopic sinus surgery to be performed in this population. It is rare for them to develop the extent of disease that would require surgical intervention, and surgery, in fact, is often avoided as the sinuses have not fully developed in the pediatric population. Furthermore, they are unable to provide their own informed consent to participate in this trial.

e. Stanford Populations

NA

f. Healthy Volunteers

NA

g. Recruitment Details

Recruitment will be invitation only from the patient population seen in our Rhinology clinics. Patients will first be evaluated by our providers. If, based on that evaluation, endoscopic sinus surgery is recommended to them and they meet inclusion criteria, they will then be informed of the study and its purpose and importance. After this has been discussed, patients will be invited to participate if they so choose. Our nurse practitioner performs all study introductions and obtains consent. If there are any questions, Rhinology providers are always available for consultation. We do not intend to advertise to nor recruit within the general public. There will be no recruitment materials.

h. Eligibility Criteria

i. Inclusion Criteria

Age > 18 Able to provide informed consent Chronic rhinosinusitis with or without nasal polyposis based on published diagnostic criteria Patients undergoing endoscopic sinus surgery

ii. Exclusion Criteria

Age
Aspirin exacerbated respiratory disease
Allergic fungal sinusitis
Cystic fibrosis
Immunosuppression
Chronic steroid use
Steroid use within 30 days prior to surgery

i. Screening Procedures

Screening will be performed during clinic visits. First, it must be determined if a patient is a surgical candidate, which is a decision based on establishing the diagnosis of chronic rhinosinusitis by published diagnostic criteria. Furthermore, patients with this diagnosis must have failed maximum medical therapy. At the pre-operative appointment, a complete routine history will be taken as is standard in our clinics. This will include information regarding past medical history, past surgical history, current medications, social history, family history, and allergies. This information is readily available to us as a part of the electronic medical record. Patients must also confirm accuracy by filling out a questionnaire prior to their first encounter. No qualifying laboratory values are necessary.

j. Participation in Multiple Protocols

We do not anticipate that participants will be enrolled in more than one study. However, we will be sure to inquire before enrolling patients if they are actively participating in another study. If so, and our interventions may interfere in any way, we will not continue with the enrollment

process. We do not anticipate difficulty in recruiting the required number of patients, and, therefore, will defer to studies in which patients are already enrolled.

k. Payments to Participants

NA

l. Costs to Participants

The participant will accrue identical costs to any patient being evaluated and treated for chronic rhinosinusitis, which will vary tremendously based on insurance policies. During the process, costs that may accumulate include: clinic appointments, prescribed medications, surgical intervention, specialty evaluation. No additional costs will be charged based on participation in this study.

m. Planned Duration of the Study

The study duration is anticipated to be 12 months. Time allotted for screening of the participant will depend heavily on the time that elapses between the initial patient encounter in clinic and the date for which surgery is scheduled. This may require 1-6 months, and occasionally longer. Active study participation will begin at the surgical date and end at the 4th post-operative visit. Organization and analysis of the data will require 2-4 weeks.

6. RISKS

a. Potential Risks

i. Investigational devices

NA

ii. Investigational drugs

NA

iii. Commercially available drugs, biologics, reagents or chemicals

Oral Prednisone: The side effects of short courses of systemic steroids (<3 weeks) include stomach upset, weight gain, insomnia, hyperglycemia, hypokalemia, adrenal suppression, and mood changes. These can occur in up to 16% of patients, with stomach upset being the most common. These effects are all reversible after stopping the steroid. Topical Fluticasone: The side effects of topical steroids include dry throat, sore throat, nasal irritation, headache, nose bleeds. These are the more common side effects, the incidence of which is unknown. Rare and serious side effects include difficulty breathing, flu symptoms, and vision changes. Again, these typically improve after stopping the steroids. On very rare occasion, vision symptoms may be permanent. None of these interventions differ from those already being instituted by our staff.

iv. Procedures

See the risks of the commercially available drugs - None of these interventions differ from those already being instituted by our staff.

v. Radioisotopes/radiation-producing machines

NA

vi. Physical well-being

NA

vii. Psychological well-being

NA

viii. Economic well-being

NA

ix. Social well-being

NA

x. Overall evaluation of risk

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

b. International Research Risk Procedures

NA

c. Procedures to Minimize Risk

Medication administration will be monitored during the post-operative visits. Patients will begin their assigned therapy the day after surgery, and then will be seen 1, 2, and 4 weeks post-operatively. Any side effects being encountered will be discussed at these visits, and specialty services available in a timely manner to address them if needed. Furthermore, patients have 24 hour access to a physician in the department, and are, at any time, able to call with questions or concerns regarding their treatment.
Identifiable patient information will be handled per institutional protocol. Unique login information is required for all persons wishing to access the electronic medical system. All communications with patient data are sent on a secured machine via an encrypted service that is password protected.

d. Study Conclusion

The study will officially terminate for each patient after the 4th post-operative visit.

If a patient is experiencing an adverse outcome from surgery or from post-operative therapy, their participation in the study will be terminated early in the interest of well-being. In this event, patients will be promptly seen in subspecialty clinics (or by inpatient consultants if the patient is

admitted to the hospital) that may assist in managing these complications. Additionally, if a patient is having an emergency, they are able to contact one of our house staff 24 hrs per day for advice. As a last resort, our Emergency Department is available for expedited work up of major events.

Finally, if it becomes clear after the first 50 patients have completed their interventional therapy that one therapy arm is drastically superior to others, and that patients are thus not receiving optimal care, the study will be terminated and therapies altered.

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e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

Aggregate Data Analysis Reports Progress toward study endpoints AEs, SAEs, SUSARs

ii. Person(s) responsible for Data and Safety Monitoring

The Protocol Director will be responsible for Data and Safety Monitoring.

iii. Frequency of DSMB meetings

NA

iv. Specific triggers or stopping rules

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v. DSMB Reporting

NA

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Y

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

N

f. Risks to Special Populations

NA

7. BENEFITS

The current standard of care in the management of CRS patients with and without nasal polyposis after endoscopic sinus surgery involves a non-standardized regimen of antibiotics and systemic steroids. However, the use of oral steroids in this period is based on anecdotal evidence and expert opinion (level IV evidence). Given the known risks of oral steroid use, it is important to definitively establish their utility and to investigate alternatives. Our study first seeks to more clearly define the role of steroids, both oral and topical, in the perioperative setting. Furthermore, we intend to establish topical steroids as a safer but equally effective therapy. This information will be invaluable to the field and practice of Rhinology. There is a great need for additional investigation to determine whether steroids truly have a beneficial role in post-operative CRS patients. We endeavor to provide randomized, controlled data on which clinicians may base their therapeutic decisions. In addition, the introduction of topical steroids into routine post-operative care would fundamentally change current clinical practices, and may even influence future guidelines. For patients, this may transform their post-operative care into one that is more easily tolerated with less detrimental effects on health.

8. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.