Randomized Controlled Trial of Preoperative Steroids in Autoimmune Thyroid Disease

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Abbreviations:

AE = adverse event

ATA = American Thyroid Association

Ca = Calcium

FT4 = thyroxine

HIPAA = Health Insurance Portability and Accountability Act

Ig = Immunoglobulin

PHI = protected health information

PTH = parathyroid hormone

QoL = quality of life

RAI = radioactive iodine

RLN = recurrent laryngeal nerve

SAE = serious adverse event

SF-12 = 12 question Short Form Health Survey

TgAb – Thyroglobulin Antibody

ThyPRO = thyroid-specific quality of life patient-reported outcome measure for benign thyroid disorders

TNF = tumor necrosis factor

TPO – Thyroid peroxidase antibody

TRAb – Thyrotropin Receptor antibody

TSI – Thyroid Stimulating Ig antibody

TSH = thyroid stimulating hormone

Project Summary:

Graves' disease and Hashimoto's thyroiditis are autoimmune conditions affecting the thyroid gland. Surgery to remove the thyroid gland in these patients may be complicated by the inflammatory nature of these diseases. Prednisone is a steroid medication used to decrease inflammation of the thyroid gland in other disease states such as sub-acute thyroiditis, but has not been used systematically to reduce inflammation in patients about to undergo surgery. This is a small pilot project that proposes to randomize a small sample of patients about to undergo surgery for their autoimmune, inflammatory thyroid disease, and determine if a short course of prednisone alters the inflammation of the gland and makes surgery less difficult. This could potentially lead to better outcomes for these patients, as well as increased time to recovery and improved quality of life. This project proposes to administer short quality of life surveys at three time points, as well as draw additional labs to measure antibody levels at times when patients will already be getting labs drawn for clinical purposes. The purpose of this study is to generate preliminary data from which a larger, blinded, placebo-controlled trial could be designed.

Background and Significance:

Graves' disease and Hashimoto's thyroiditis are conditions increasingly being treated with surgery. High circulating auto-antibody levels in these diseases are correlated with lower quality of life (QoL) regardless of thyroid hormone status[1-3]. A recent randomized trial for patients with euthyroid Hashimoto's disease showed improved QoL and antibody clearance than patients treated with levothyroxine alone[4]. Surgical complications of hypocalcemia and recurrent nerve palsy may be higher in autoimmune thyroid conditions as compared to thyroidectomy for benign nodules or cancer[5], and this is commonly attributed to the greater difficulty of the operation because of increased size and inflammation of the thyroid gland[6].

Some clinicians hesitate to recommend thyroidectomy for autoimmune disease without some other indication (such as compressive symptoms or indeterminate nodule) because of this increased risk of complications. However, the benefit to patients in terms of QoL and antibody-mediated symptoms resolution may be much greater[7] and sustained for these patients than previously understood. Instead of focusing on comparing complications rates for different indications for thyroid surgery, research is needed to develop strategies that can decrease the inherent technical challenges and thus improve surgical outcomes specifically for these inflammatory autoimmune conditions.

A course of steroids is an accepted and proven treatment to calm inflammation in patients with subacute thyroiditis[8]. There is low quality and anecdotal evidence that administering high-dose steroids in the perioperative period may make thyroid surgery easier to perform, and the American Thyroid Association (ATA) guidelines recommend using steroid in the rapid prep of Graves' thyrotoxicosis[9], but whether steroid prep translates into improved surgical outcomes or improved time to recovery after surgery for patients with autoimmune thyroid disease is not known. The lack of good data in this area represents a *critical deficiency in the care of patients with autoimmune thyroid disease*. Emerging data on the benefits for surgery in this population will continue to expand the indications for surgery; consequently, there is an *urgent need* to

understand the effects of the use of steroids in the preoperative period on outcomes for patients with autoimmune thyroid disease.

We will be administering a medication to patients – prednisone – which is not a new drug and is not investigational. It is an accepted treatment of patients with subacute thyroiditis at similar doses to what we are proposing. The regimen recommended by the ATA guidelines for treatment of subacute thyroiditis is: Prednisone 40mg x 1-2 weeks followed by gradual taper of 2-4 weeks[9]. We propose that the anti-inflammatory effects of this medication that we know are effective in non-surgical thyroiditis patients will be beneficial in the immediate pre-operative period.

Physical Risks

Prednisone is a common medication prescribed often for inflammatory conditions. A recent review found that 1 in 5 adults in this country over 3 years received at least 1 prescription for short term use of corticosteroids for various conditions such as allergies, respiratory tract infections[15]. Long term use is associated with severe risks such as fungal, viral or opportunistic infections, poorly controlled blood glucose, avascular necrosis, fracture, hypertension, weight gain, poor would healing, venous thromboembolism, and risks to a fetus in pregnancy. Risks of a short course are generally low, as the risks are dose and duration dependent. Risks of a short course (1 week) of prednisone include elevated blood sugar, increased risk of infection, venous thromboembolism, and bone fractures. The absolute risks in one well done study showed that the 90-day risk of a hospitalization for sepsis after a <30 day course of corticosteroids was 0.05% compared to 0.02% for non-users. Risk of venous thromboembolism was 0.14% compared to 0.09% of non-users, and risk of fracture was 0.51% compared with 0.39% of non-users. Additionally, there may be side effects of taking the medication such as nausea, gastrointestinal upset, appetite changes, mood changes, or insomnia. The risk of wound infection for thyroid surgery is low – less than 0.5%, and we will exclude pregnant patients, patients with diabetes who are at higher risk of elevated blood glucose, and patients with other immunocompromised states.

Specific Aims/Study Objectives:

We hypothesize that administering a course of steroids to patients with Graves' or Hashimoto's thyroiditis prior to thyroidectomy will result in a less difficult thyroid operation (measured by a previously validated scale) and a lower rate of surgical complications. Furthermore, we hypothesize administering steroids will results in faster improvement in antibody levels, antibody mediated cytokine levels, and health care quality of life as measured by surveys.

Over the past 5 years, our group has performed nearly 350 thyroidectomies for Graves' or Hashimoto's thyroiditis, giving us nearly 70 potential subjects per year. We have extensive qualitative methods experience and ability to collect QoL data from our recent clinical trial on prophylactic central neck dissection for patients with differentiated thyroid cancer. We developed and validated an instrument to quantify the difficulty of thyroid surgery. This project will be a small pilot that is a non-blinded, randomized trial of patients of glucocorticoids in patients about to undergo surgery for autoimmune thyroid disease. The primary aim of this pilot is really feasibility for the definitive trial: determining willingness of participants and clinicians to

enroll, rates of follow up and response to questionnaires, and time needed for recruitment, collection of data and analysis. The specific aims are for the larger, definitive trial, but will be assessed for this small pilot.

These specific aims are:

- **Determine the benefits and safety of preoperatively administered prednisone for patients with autoimmune thyroid disease undergoing thyroidectomy on:**
    - **Difficulty of surgery[6,10] and rates of surgical complications**
    - **Serum autoantibody levels**
- **Longitudinally assess the impact of surgical treatment on QoL in patients with autoimmune thyroid disease**

Outcomes:

- Primary
    - Thyroid difficulty Scale score
    - Autoantibody levels
    - QoL scores (12 question Short Form Health Survey [SF-12], thyroid-specific quality of life patient-reported outcome measure for benign thyroid disorders [ThyPRO])
- Secondary
    - Ultrasound doppler quantification of blood flow
    - Surgical complications (parathyroid hormone [PTH] level, recurrent laryngeal nerve [RLN] injury)

Research Design and Methods:

- Study population = 30 patients with autoimmune thyroid conditions referred to the University of Wisconsin endocrine surgery clinic for surgical management. Patients will be invited to join the study after the decision has been made to proceed with thyroidectomy as the clinical treatment of their autoimmune thyroid disease. Once they have decided to proceed with surgery, we will describe the study rationale and the risks and benefits to enrolling. We will explain that patients will be randomized to take steroids for 1 week prior to surgery, in addition to other medications that we give all patients before surgery. If they choose not to enroll in the study, their thyroidectomy will proceed as planned. For the study, 15 patients will be treated with steroids for 1 week prior to surgery, 15 will not receive steroids. Both otherwise receive the current standard of preoperative care. We are doing a stratified randomization in blocks of four within four groups of patients, as determined by category of diagnosis (Graves' vs. Hashimoto's) and BMI (<35 vs >=35). The small block size will allow for equal numbers of control and treatment subjects even if category sizes are small.
    - Inclusion Criteria: Graves' disease or Hashimoto's disease with positive thyroid autoantibodies (Thyroglobulin Antibody [TgAb], Thyroid peroxidase antibody [TPO], Thyroid Stimulating Ig antibody [TSI], and/or Thyrotropin Receptor antibody [TRAb]). This information is found in the patient's medical record which is available at the time of surgical consultation. If a patient has not had antibody levels checked prior (this is rare), we can discuss the trial with the patient and draw the first set of clinical and research labs. If the clinical labs return that antibody levels are negative, we will inform the patient that they are not eligible to participate and will withdraw them from the study and discard the

research serum sample. All patients must first agree to undergo total thyroidectomy for their disease before they are even approached about the trial.
        - Exclusion Criteria: Pediatric patients < 18. Prior treatment with radioactive iodine (RAI). Known diagnosis of thyroid cancer. Diabetic patients. Patients on any immunosuppressive regiment (such as organ transplant patients or patients treated for other autoimmune condition). Pregnant patients. Patients being treated for active infection. Any patient for whom the surgeon feels steroids would provide a clear benefit (ie. Extremely high auto-antibody levels with a very large, inflamed thyroid gland) will be treated according to the clinical judgement of the surgeon. If a surgeon feels steroids are indicated and prescribes them, the patient will not be eligible for the trial.
        - Subject identification and recruitment. We will identify patients from our own clinic who have been referred to us for consideration of thyroidectomy as treatment for their autoimmune thyroid disease. Each surgeon spends time prior to each clinic looking through their patient list, and will flag anyone with an autoimmune thyroid disease coming to discuss thyroidectomy as a potential study participant. After the normal clinical consult, those patients who choose to undergo thyroidectomy and otherwise meet criteria will be given the opportunity to participate in the trial. This will all occur in the same physical setting of our UW endocrine surgery clinic.
    - Because this is a small pilot study done with limited resources and designed for feasibility and generating preliminary data, patients and surgeons will not be blinded to treatment. The operating surgeon is typically the provider who does the preoperative assessment and provides medications and instructions directly to the patient, and we lack the resources to coordinate a study-specific preoperative visit.
        - Because participants are not blinded, knowledge of their group assignment may affect their behavior. Subject non-blinding should not affect our primary outcomes of thyroid difficulty, serum antibody, or cytokine levels. It may alter their responses on the QoL surveys, however, as steroids can cause a euphoric effect while a person is taking them. QoL surveys are to be administered before the study begins, and then not again until 6 weeks and 6 months after surgery when subjects are no longer taking the steroids, so the effect will be minimal. For secondary outcomes, subject non-blinding should not affect ultrasound measurements or surgical outcomes.
        - Because surgeons are not blinded, it is possible that their responses for the thyroid difficulty scale will be altered by their knowledge of whether the subject took steroids. The logistics of having the patients leave the surgeons clinic not knowing their group assignment, then having a different researcher assign and provide the medication would be beyond the budget and capabilities of our team for this feasibility trial. We feel the benefits of ease of enrollment and ability to recruit sufficient patients outweigh the possible bias in the thyroid difficulty scale.
    - There are no additional collaborating sites – this will all be performed at UW Hospitals and Clinics
    - Identify information extracted from medical records – demographics, length of time of disease, lab values related to thyroiditis disease, indications for surgery,

surgical data including blood loss and length of operation, postoperative laboratory values related to thyroiditis.

- We know that glucocorticoids may decrease Immunoglobulin (Ig)G and IgA levels with moderate-to-high dose steroids given over short term. (10-20 percent at one week in rheumatoid arthritis patients)[13], therefore we intend to collect serum for antibody levels at intervals more frequent than our standard of care.

- **Specimen/data collection, handling, storage**
  - Data will be collected electronically (REDCap) on the Institute for Clinical and Translational Research (ICTR) secure version of the software and on paper. The only data recorded on paper will be the Thyroid difficulty scale and the prednisone compliance survey and these will be stored in the PI's office in a locked file cabinet.
  - All information obtained and associated data files will be confidential and will be kept in a locked file or password protected secure departmental server through the department of surgery (U:). This server is backed up according to standard protocols. All computers used to access this server are password protected. The risk of breach of confidentiality regarding participation in the study outside of the scope of the research will be handled by carefully controlling access to study data only to personnel on the research team.
  - Confidentiality will be protected further by: (1) using a participant log form that contains only the minimum necessary protected health information (PHI) concerning participants, and storing this log in a locked area when not in use, (2) not sharing PHI with any outside institution, (3) coding data collection forms with a consecutive participant number that is not derived from any participant personal identifiers, and linking that data collection form to the participant log, and (4) storing the participant log, the key linking the code to the PHI, and data collection forms separately.
  - It is highly likely that these measures will result in avoidance of breach of confidentiality outside of the research. In addition, the data to be collected are not sensitive to participants.

- **Study Procedures**:
  - <u>Eligible patients</u> will have a diagnosis of autoimmune thyroiditis, positive auto-antibodies, and an indication or preference for surgical treatment with a total thyroidectomy. This will be a randomized, non-blinded pilot study, and all patients who are eligible will be given the opportunity to participate.
  - <u>Preoperative Testing:</u> All randomized patients will undergo our current standard of care pre-operative testing, which includes a clinic ultrasound and laboratory testing of thyroid function and autoantibody levels. All study patients will be directed to complete the online quality of life surveys (SF-12 and ThyPRO) prior to surgery. Each survey will take approximately 10-20 minutes to complete. Patients randomized to the steroid arm will be given a prescription for prednisone 20 mg daily for 7 days prior to surgery. Patients will be instructed to take the prednisone once a day, in the morning, with food. All patients (steroid or not) will receive our standard instructions for TUMS and saturated iodine (in Graves' disease) if indicated. Our current standard of care for patients with Graves' disease is to take 1-2 drops of saturated iodine solution

twice a day and 1000mg of TUMS three times a day for the 7 days leading up to surgery. There is no consistent regiment for TUMS or saturated iodine for patients with Hashimoto's in our clinic, but it is up to the clinical judgement of the surgeon whether to use these medications on an individual basis. There are no interactions of these medications with prednisone, and administration or non-use of these medications does not exclude anyone from participating in the trial.

- Day of Surgery*:* Surgeon will repeat the ultrasound in the operating room to compare area of blood flow. As part of the clinical workup, each surgeon always performs thyroid ultrasound using our GE Logiq clinic equipment, and this includes a single image using "doppler" mode to measure blood flow. Surgeons then do an ultrasound once the patient is positioned in the operating room to verify incision placement, and for study patients we will save one "Doppler" image for comparison purposes to the preop image. While the single image is unique to this study, performing the ultrasound is part of our routine clinical care and saving one additional image takes 10 seconds and confers no additional risk. There is no charge for this image and it will be uploaded with the clinical image to the radiology digital storage system for the surgeons to compare blood flow from before and after steroid administration. Research specific blood draw (15mL) will occur at the time of IV placement and sent for antibody levels. Patients will be asked whether they took their course of steroids as described and we will record their answers. If they report not taking it as directed, their narrative reasons for not doing so will be recorded. Total thyroidectomy will be performed using standard techniques in all patients potentially eligible for randomization. An open technique will be used to remove the entire thyroid including pyramidal lobe and all visible thyroid tissue. Care will be taken to visualize and preserve both recurrent laryngeal nerves and to preserve all parathyroids in situ. All removed specimens will be carefully examined for any parathyroid tissue and any devascularized or resected normal parathyroid glands will be confirmed by frozen section and autotransplanted into the sternocleidomastoid muscle, as per our standard of care. The surgeon will then fill out the "Thyroid Difficulty Scale" at the conclusion of the operation, either by the surgeon entering it directly into the secure RedCap project or recording their answers on paper that is coded and entered later. If on paper and coded, surgeons will store the paper separately from any PHI related to that subject and will destroy the paper as soon as it is entered into the database.
- 2 weeks postoperatively: Patients are all seen in clinic 10-14 days after surgery and calcium and PTH hormone levels are checked as per our standard of care. Research specific labs of antibody levels will be checked for our study patients (15-45 mL, depending on individual antibody profiles of subjects).
- 6 weeks postoperatively: Patients are all given a lab slip to have thyroid stimulating hormone (TSH) and thyroxine (FT4) drawn to check levothyroxine dosing as per our standard of care, as well as checking antibodies to monitor for treatment success. This can be done at a lab of their choosing. Patients will be sent an electronic link to fill out the quality of life surveys (SF-12 and ThyPRO).

- 6 months postoperatively: Patients have TSH and FT4 drawn again to check levothyroxine dosing as per our standard of care, as well as checking antibodies to monitor for treatment success. Again, this can be drawn at the lab of their choice. Patients will be sent an electronic link to fill out the quality of life surveys (SF-12 and ThyPRO).

Time point	Procedures (all standard of care)	Labs (*italics are current standard of care,* black are study specific and in the budget)	Surveys (study specific)
Preop clinic visit (2-4 weeks preop)	Ultrasound with color doppler quantification of blood flow, vocal fold ultrasound	*Ca, PTH, TSH, FT4, Tg, TgAb, TSI, TPO, TRAB*	SF-12, ThyPRO
Day of Surgery	Repeat ultrasound with color doppler	TgAb/TPO/TSI/ TRAB for any that were positive preop	Thyroid difficulty scale (surgeon)
2 weeks postop	Clinical voice assessment, vocal fold ultrasound	*Ca, PTH,* TgAb/TSI/TPO/TRAB if they were positive	
6 weeks postop	Laryngoscopy if clinically indicated	*TSH, FT4, Tg, TgAb/TSI/TPO/TRAB if they were positive*	SF-12, ThyPRO
6 months postop		*TSH, FT4, TgAb/TSI/TPO/TRAB if they were positive*	SF-12, ThyPRO

- **Study Drug:**
  - Rx will be provided to patients randomized to steroid prep group for "Prednisone 20mg tabs. Sig: Seven days before your scheduled surgery, Take 1 tab (20mg) daily in the morning for 7 daysTake with food. Disp: 7 tabs. Refills: none"
  - Patients will fill this at the UW American Center outpatient pharmacy at no charge, no drug accountability procedures are required for this commercially available drug that is being used in the standard of care dosing and route.
  - Concomitant medications allowed/disallowed: No other steroids or immunosuppressive medications, No antibiotics, antitubercular drugs, or anti-fungals. No anticoagulants. Caution in many anti-seizure medications.
  - No placebo
  - While chronic systemic steroids may impair wound healing, there is literature to support that acute (< 10 days), high-dose systemic corticosteroid use has no clinically significant effect on wound healing[14]
  - The prednisone dose is within the accepted guidelines for rapid prep for Graves' disease patients, and is considered a moderate dose. It is expected to contribute negligible increased risk for wound complications in this population where wound infection rates are already extremely low (less than 0.5%).
- Data and Safety Monitoring Plan:
  - This is a study that involves randomizing patients to receive a prescription drug, therefore is greater than a minimal risk study. It is using a commonly prescribed medication for a short duration and has been shown to have a low incidence of adverse events at these doses and durations. Prednisone is already prescribed

in a subset of similar patients to our population outside the context of a trial (Graves' disease requiring rapid surgical prep). Potential problems will be monitored and handled by the primary surgeon, clinic staff and principal investigator. This is appropriate given the small number of participants (15 subjects will receive the intervention drug), single site, and low risk medication. We will not assemble a formal *external* Data and Safety monitoring committee..

- Dr. Elfenbein will be notified by the enrolling surgeon each time a subject enrolls in the trial and of any protocol deviations. Adverse events from the study medication will be reported immediately. We anticipate that the manner in which subjects will report adverse events is by (1) directly notifying the principal investigator as directed in the informed consent document, (2) calling our clinic staff who will notify Dr. Elfenbein, or (3) by reporting side effects and amount of drug taken on the drug compliance survey on the day of surgery.
- Protocol violations and deviations, side effects, and adverse events will be noted in the secure RedCap database.
- A monthly clinical research meeting occurs among our group to discuss all clinical research, and this study will become a standing item on our agenda during the duration of the trial for any surgeon to discuss possible adverse events or concerns
- Given low rates of wound infection in this population, any wound infection requiring treatment with antibiotics in the steroid group will be considered an adverse event (AE) and will be investigated immediately by the principal investigator and operating surgeon, and reported to the IRB within 14 business days If a wound infection requires an operation, it is considered a serious adverse event (SAE), although it is not immediately life threatening or debilitating to other subjects, so also will be reported with 14 business days to the IRB. If a second wound infection requiring antibiotics or surgery occurs in the steroid treated group, enrollment will immediately cease and it will be reported as a SAE in the same 14 day timeframe, when we will closely scrutinize these cases with the help of the IRB to determine whether it is safe to proceed. Monitoring for wound infections will occur in the context of our usual clinical care. We will see every wound in person at the postoperative visit, but otherwise we rely on patients self-reporting to alert clinic staff if they have concerns (redness, warmth, drainage) about their incisions. No specific study-specific instructions will be given to study subjects, we will simply ask them to call the clinic staff if they have any concerns, and clinic staff will be trained to immediately notify Dr. Elfenbein if a study patient reports wound complications.

- Statistical Considerations: Provides an explanation as to why the number of subjects was chosen and the means for analyzing data will meet the specific aims/study objectives
  - As a small pilot, feasibility study, the size of 30 is based on our estimate of a realistic recruitment rate for the future definitive trial. We see approximately 70 potential subjects in our clinics per year, and our listed exclusion criteria are rare in our population. We estimate that fewer than one fourth will not meet criteria, and an additional one fourth may decline to participate. From the patient perspective, enrollment involves only answering QoL surveys and possibly taking a medication 1 week prior to surgery, the risks and effort are not much greater, which is why we estimate a generous rate of inclusion. We are giving ourselves 1 year to enroll all 30 patients (with an additional 6 months to collect follow up data). Our biostatistics team has already been engaged and feels this is an aggressive but realistic expectation. For all primary aims, data will be analyzed

using a mixed model two-way analysis of variance examining the effects of the treatment group. When appropriate, t-tests comparing the steroid prep vs non-steroid prep groups will be performed. Our WISOR biostatistics core will perform this analysis using SAS statistical software. This supplemental data analysis will then be used to obtain a sample size calculation for our future study.
    - There is no planned interim analyses for this short study
    - The data will be analyzed in an "intent-to-treat" fashion with groups being analyzed based on their initial group and not on whether or not they report taking the steroid medication. However, if large numbers of patients report not taking the medication as directed, this is very important information for our future larger study and we will record patient responses and reasons for this.
    - Drop-outs are not expected in high numbers for this population. Everyone who undergoes thyroidectomy requires levothyroxine therapy postoperatively, and we follow all of our patients very closely for at least 6 weeks. It is possible that the 6 month data will be more challenging to obtain, and that is also very important information to know in this feasibility trial.
- Data and Record Keeping: Addresses how data will be captured, protected, and shared with others
    - The Principal Investigator will manage the study data
    - Data confidentiality will be assured by coding and storing electronic data on password protected Department of Surgery servers, storing coding keys and data separately, as previously described. Data will be destroyed 10 years after publication of study findings.

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