Research plan/Protocol for HRO:
Further use of biological material and health-related personal data for research pursuant to Articles 32 and 33 HRA

Title of the research project

Thyroidectomy for Graves' Disease or Amiodarone-induced Thyrotoxicosis: Is it still necessary to achieve a preoperative euthyroid state? – A prospective observational multicenter European study

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Confirmation of the project leader and the sponsor

With my signature, I attest that all information in this protocol is correct and that I will comply with the information I have given and with national legislation, namely data protection law.

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Abbreviations

HRA	Human Resarch Act
HRO	Human Research Ordinance
AIT	Amiodarone-induced Thyrotoxicosis
EU	European Union
TSH	Thyroidea stimulating Hormone
fT3	free triiodothyronine
fT4	free thyroxine
ICU	intensive care unit

1. Background

Thyrotoxicosis is the clinical condition associated with excessive thyroid hormone activity, usually due to inappropriately high levels of circulating thyroid hormones. The clinical presentation is variable, ranging from asymptomatic to life-threatening 'thyroid storm'. Symptoms include weight loss, heat intolerance and palpitations [1].

Thyrotoxicosis can result from diffuse alterations of the thyroid gland, such as Graves' disease and Amiodarone-induced thyrotoxicosis (AIT). This poses a considerable challenge across multiple medical specialties, spanning endocrinology, cardiology, and anesthesiology.
Graves' disease is a widespread endocrine disorder that affects approximately 1% of the population. Treatment strategies vary based on clinical presentation and patient preferences, with options ranging from medical management to thyroidectomy [2,3].
Amiodarone is a class III antiarrhythmic drug used to treat supraventricular and ventricular arrhythmias, and to maintain sinus rhythms after cardioversion of atrial fibrillation [4]. Its prescription has become more common in recent decades. However, the medication comes with the risk of precipitating severe thyrotoxicosis, which, if left untreated, can be fatal. [2, 4, 5, 6]. Discontinuing the medication may not always be feasible.
Under medical treatment for thyrotoxicosis (using thionamides or glucocorticoids), attaining euthyroidism can frequently be challenging to achieve, prompting consideration of definitive treatment through thyroidectomy [7,8].
Thyroidectomy for Graves' disease or AIT presents unique disease-specific challenges, potentially resulting in elevated perioperative complication rates when compared to other indications [8]. According to current guidelines, it is recommended to attain a euthyroid state prior to surgery to mitigate perioperative risks, despite the inconclusive evidence supporting this approach [2]. Nevertheless, data from retrospective studies show that between 21-51% of patients undergo surgery when euthyroidism is not stable or cannot be achieved [9-12].
The EUROCRINE® registry offers a valuable opportunity to assess the morbidity linked to thyroidectomy for Graves' disease and AIT, considering both euthyroid and hyperthyroid states. This prospective, observational study aims to refine surgical protocols and inform updates to existing guidelines, thereby advancing the management of thyroidectomy for Graves' disease and AIT.

2. Objectives

The aim of this study is to explore potential differences in the morbidity of thyroidectomy for Graves' disease and AIT based on thyroid metabolic status prior to or during the procedure. Our hypothesis suggests that there will be no significant differences in relevant complication rates, such as transient and permanent nerve palsy, transient and permanent hypoparathyroidism, reoperation, severe adverse intraoperative cardiac events, or the onset of a "thyroid storm" [13-15].
If this hypothesis is confirmed, patients with Graves' disease and AIT who are scheduled for thyroidectomy would no longer need to wait to reach a state of euthyroidism. This would streamline preoperative assessments and expedite surgical planning, leading to reduced costs and shorter waiting times, and minimizing exposure to dangerous and excessive levels of thyroxine.

The primary endpoint is the relevant complication rate in both groups: transient and permanent nerve palsy, transient and permanent hypoparathyroidism, reoperation for postoperative haemorrhage, and occurrence of a “thyroid storm".
Our secondary endpoints are results of other complications, duration of surgery, estimated blood loss, intraoperative tachycardia, length of hospital stay, ICU monitoring, preoperative medications, use of autofluorescence, angiofluorescence, and neuromonitoring, preoperative calcium and/or vitamin D supplementation, clinic volume.

3. Design

We are planning a prospective, observational, multicenter, multinational study based on the EUROCRINE® registry. Eurocrine® is an international endocrine surgical quality registry based in the EU. The project will be a Swiss national and multinational multicenter study.
Several other in Eurocrine® participating, international clinics have agreed to participate in the study. It is planned that a total of around 25 clinics in various European countries will take part in the study. In a first step, the participating centers in Switzerland will be opened.
The data will be prospectively entered into the registry online in encrypted form, as is usual with the Eurocrine® registry. For the EUORCRINE registry itself a declaration of no objection has been issued in May 2017 (2017-00683). The clinics participating in our study do this part of the data entry as before. The participant can then be enrolled in the study via a my-Eurocrine add-on module and additional study-specific routine data can be collected directly in the Registry online platform. All variables, along with the study-specific variables, are systematically collected in the centers as a component of patient care, since these parameters are essential for treatment. The operation itself, the preoperative or postoperative treatments are not altered in any way. Information about postoperative complications will be registered at the Eurocrine database as previously implemented.

Patients with Graves' disease or AIT can be included in this study and will be assigned to two groups. We rely on free triiodothyronine (fT3) and free thyroxine (fT4) levels to assess functional status since the TSH level may not accurately reflect the patient's true functional status. Patients will be classified as uncontrolled if their levels of fT3 or fT4 are elevated, or as controlled (normal fT3 and fT4) immediately prior to surgery (normal ranges for all ages: fT4 12.0 - 22.0 pmol/l; fT3 3.1 - 6.8 pmol/l). The fT3 and fT4 tests will be conducted no more than one week before surgery. Consecutive patient enrolment is necessary to accurately reflect real clinical conditions. The standard variables are recorded as usual, with the addition of the study-specific variables (see CRF). All complications will be documented to evaluate the risk of surgery in both controlled and uncontrolled metabolic states.
For diagnosing patients with "thyroid storm", we opted to utilize the established Japanese Association classification [13], which is deemed more suitable for clinical settings compared to the "Burch and Wartofsky" scale [14].

4. Origin of the data/biological material

We want to analyze data routinely collected in the clinical practice for adult, non-pregnant patients who underwent surgical management of Graves ' disease and AIT in different functional states. The variables are summarized in the CRF (refer to CRF).

All data will be collected in the Eurocrine database with the standard module and an add-on specific variable my-Eurocrine module for study specific routine data. All participating sites will use the Eurocrine database and collect their data prospectively online and in a coded form. In the Eurocrine data register, data is routinely recorded up to six months postoperatively in the event of complications occurring during treatment. This period also corresponds to that of our study project.

We plan to run the study for 2 years and will start as soon as a positive ethical decision has been made. If enough patients have been enrolled before the end of the 2 years, the study will be stopped early.

5. Inclusion criteria

- Adult patients (≥ 18 years of age) undergoing surgical treatment for Graves' disease or Amiodarone-induced thyrotoxicosis (AIT) with biochemically confirmed hyperthyroidism or on specific medication for the treatment of Graves' disease or AIT.
- Patients providing signed informed consent.

6. Exclusion criteria

- Children and minors (<18 years).
- Pregnant women.
- Patients unable or unwilling to provide informed consent due to language barriers or intellectual limitations.
- Patients undergoing concurrent parathyroidectomy for primary or secondary hyperparathyroidism, lymph node clearance, or redo surgery.
- Surgical procedures performed for other reasons than Graves' disease or AIT

7. Information and consent of participants

We will collect and analyze data routinely collected in clinical practice. The consent procedure at all Swiss sites are as followed:

- Patients are informed through our documents entitled <General consent for the re-use of health-related data and samples for research purposes.> (refer to the attached documents for all Swiss clinics except for hospital Männedorf). All study patients provide approved informed consent for the further use of their medical records and tissue samples using the general document from the Hospital
- For clinics that do not have general consent for their clinics (e.g. Hospital of Männedorf and clinics abroad), the Eurocrine consent form is used as standard (German and English versions available, refer to attached documents).
- If a patient does not agree to the General Consent of the Swiss sites using the General Consent, but agrees to the use of data related to the thyroid disease and treatment, the patient can be enrolled in the study by signing the Eurocrine Consent.

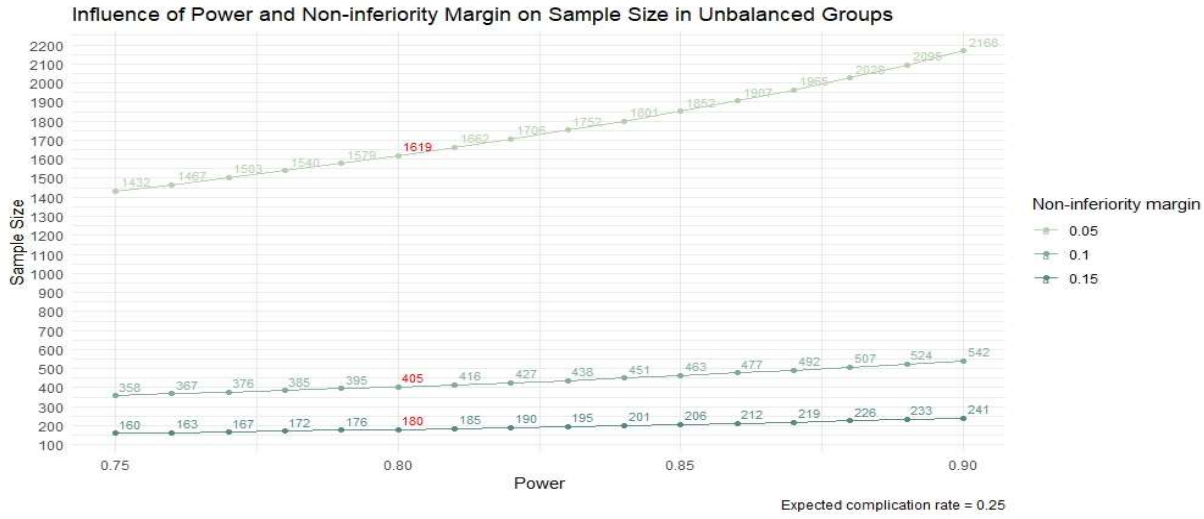
8. Scientific methods and sample size

As of March 2024, the European registry for endocrine surgery, EUROCRINE®, has documented 114,000 thyroid resections conducted across 141 centers in Europe. Among these, an estimated 1,800 cases per year underwent surgery for either Graves' disease or Amiodarone-induced thyrotoxicosis (AIT).

Sample Size Calculation:

The sample size for this non-inferiority study was determined based on the desired power (1-β), non-inferiority margin (δ), and expected complication rate (*p*). A significance level (α) of 0.05 was chosen for hypothesis testing. For this study, a desired power of 0.8 and a non-inferiority margin of 0.1 were selected. A different group distribution was calculated from the known group sizes of the retrospective studies [8-10], assuming a distribution of 60% for the euthyroid, controlled group and 40% for the uncontrolled group, with an error margin of 10%. With an expected complication rate of 0.25, the calculated total sample size was approximately 405 participants. The following formula for the sample size (*n*) for an unbalanced, two-sample non-inferiority test of proportions was used.

$$n = \frac{2 \cdot \left(Z_{1-\frac{\alpha}{2}} + Z_{\beta}\right)^2 \cdot p \cdot (1-p)}{\delta^2}$$



To compare patient outcomes in controlled versus uncontrolled functional states, a sample size of 405 patients is necessary based on the given assumptions. To adjust for center variability and missing data, a correction factor of 1.2 will be applied, resulting in a final sample size of 486 patients. Data collection will continue for two years or until 486 patients are included, with interim analysis after six months to confirm preliminary findings. Since slightly more European clinics are participating in the study than Swiss clinics, we assume a sample size of 230 patients for Switzerland. It must be acknowledged that this is merely an estimation, as the percentage of operations for Graves' disease and Amiodarone-induced thyrotoxicosis in relation to other thyroid operations in European clinics is not currently known.
Statistical analyses will be performed using R version 4.2.1. The descriptive analyses will comprise measures of central tendency, dispersion, and location for quantitative variables, as well as frequency distributions for qualitative variables. Logistic regression will be used to compare the complication rate (primary endpoint) between preoperative thyroid function states (controlled versus uncontrolled) and determine if it is not significantly worse than the predefined margin, while adjusting for covariates such as age, gender, comorbidities such as congestive heart disease, BMI and ASA, and clinic

volume. In addition, we will investigate a possible correlation between the occurrence of tachycardia and thyroid storm and free T3 and T4 levels. The level of statistical significance will be set at $p < 0.05$.
The basis for our sample size calculation is based on retrospective data, as no comparable studies have been published to date. Wherever possible, we based our calculations on real-world values, such as complication rates, which we calculated from the EUROCRINE database. However, there is a potential for selection bias as we will be collecting data prospectively and have no control over the actual group sizes or differences. However, with the commitment of multiple centers across Europe, we are confident that we will achieve a balanced cohort and minimize the risk of selection bias.

9. Reporting obligations

The ethics committee must be notified of any change of project leader in advance. The completion or discontinuation of the research project must be reported to the ethics committee within 90 days.

10. Data protection

Uncoded data, coding and storage of the key

The data is available in coded form from the Eurocrine registry. Every patient is coded under a unique participant number.This coded number is transmitted to the participating clinic and is stored in a secured file together with the clinic's patient identification number for internal identification of authorized personnel only. It should be noted that the intrahospital patient identification number is not transmitted to the Eurocrine Register.

For all participating Swiss and International centers:
The key to the code is kept in a secured file, available to the local study team only, as all members of this study are active in patient care in their Department of Thoracic, Visceral- and/or Endocrine Surgery. After completion of the study, the key list is stored in a secure, access-protected location at the respective hospital independently of the study team.
Project data will be handled with uttermost discretion and will only be accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project.

The evaluation of all coded data will take place in Winterthur and the study team only has access to the coded data from the Eurocrine registry. No physical data of the included patients of all other clinics will leave their clinic.

11. Information on the storage of data and samples

Data generation, transmission, storage, and analysis of health-related personal data within this project will strictly follow the current Swiss and European legal requirements for data protection. This research project will be conducted in accordance with the protocol, the Declaration of Helsinki (3), the principles of Good Clinical Practice, the Human Research Act (HRA) (2) as well as other locally relevant regulations. Coding will safeguard participants' confidentiality.

In order to facilitate the secure transfer of data extracted from Eurocrine, an invitation to transfer data is transmitted from Cantonal Hospital of Winterthur to Eurocrine via the secure data transfer portal, WebTransfer ZH (https://webtransfer.zh.ch/de/transfer).
The original file with coded data received from the Eurocrine Registry will be duplicated to avoid any alteration or deletion. This list will be stored by the project leader (Andrea Goldmann, MD, Visceral- and Thoracic Surgery, Winterthur Cantonal Hospital). A backup copy is saved in a separate, secure folder on a second access-protected drive on the KSW server.
All data will be recorded in a secure, password-protected Excel file. To be able to track all changes, the track change mode will be activated in Excel. Regularly updated and dated PDF copies of the data will be generated, each signed by the project leader. These copies will be safely store in a secured restricted location available exclusively to authorized personnel (study participants). To ensure confidentiality, data will be coded using the Eurocrine-based system.
Only surgeons directly involved in patient care, will have access to Eurocrine, secured by 2-step personal identification, will have the key. This means that the study team of one center will only have access to the code and Eurocrine patient information of their respective center.

12. Retention period

Once the study is finished, coded data will be conserved 5 years in Winterthur Cantonal Hospital.

13. Ethical and regulatory requirements

Risk-benefit assessment:
Given the purely observational nature of this project, the study does not expose patients to any harm. The study uses an already established data registry (Eurocrine®), the participating clinics are trained in the handling of patient data and security aspects and have been using the data registry for years. The study-specific additional variables module can be completed easily and with little additional effort, so we can expect a high and complete level of data entry.

The primary advantages lie in this study’s potential to optimize pre-operative management of surgically treated patients with Graves' disease or AIT.
The ability of the Eurocrine registry to achieve high case numbers with good quality data means that there is an opportunity to conduct multicenter studies to strengthen the evidence base for patient management. Until now, no prospective study has been conducted on this topic due to the large number of cases required. This is now possible and a great enrichment for our patients. We hope that the results of our study will allow us to optimize the treatment of our patients.

This project complies with the regulatory requirements of the HRA and the HRO. The prerequisite for carrying out the research project is the approval of the competent ethics committee.

14. Results / transparency / publication

The results can be generalized on a particular cohort: patients with surgically treated Graves' disease and Amiodarone-induced Thyrotoxicosis in a controlled or uncontrolled functional status.

The results will be published in a peer- reviewed journal in an anonymized form (under the form of tables and results of statistical analysis) and available on PubMed.

15. Funding / Data sharing / Declaration of interest

No funding sources are currently available. There is no conflict of interest. The project sponsor from Winterthur (Dr. Andrea Goldmann) has planned to make a publication with the results. All involved clinics will be listed as co-authors.

16. References

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