

## Efficacy and safety of preoperative preparation with Lugol's iodine solution in euthyroid patients with Graves' disease (LIGRADIS Trial): Study protocol for a multicenter randomized trial

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## ABSTRACT

**Background:** Currently, both the American Thyroid Association and the European Thyroid Association recommend preoperative preparation with Lugol's Solution (LS) for patients undergoing thyroidectomy for Graves' Disease (GD), but their recommendations are based on low-quality evidence. The LIGRADIS trial aims to provide evidence either to support or refute the systematic use of LS in euthyroid patients undergoing thyroidectomy for GD.

**Methods:** A multicenter randomized controlled trial will be performed. Patients  $\geq 18$  years of age, diagnosed with GD, treated with antithyroid drugs, euthyroid and proposed for total thyroidectomy will be eligible for inclusion. Exclusion criteria will be prior thyroid or parathyroid surgery, hyperparathyroidism that requires associated parathyroidectomy, thyroid cancer that requires adding a lymph node dissection, iodine allergy, consumption of lithium or amiodarone, medically unfit patients (ASA-IV), breastfeeding women, preoperative vocal cord palsy and planned endoscopic, video-assisted or remote access surgery.

Between January 2020 and January 2022, 270 patients will be randomized for either receiving or not preoperative preparation with LS. Researchers will be blinded to treatment assignment. The primary outcome will be the rate of postoperative complications: hypoparathyroidism, recurrent laryngeal nerve injury, hematoma, surgical site infection or death. Secondary outcomes will be intraoperative events (Thyroidectomy Difficulty Scale score, blood loss, recurrent laryngeal nerve neuromonitoring signal loss), operative time, postoperative length of stay, hospital readmissions, permanent complications and adverse events associated to LS.

**Conclusions:** There is no conclusive evidence supporting the benefits of preoperative treatment with LS in this setting. This trial aims to provide new insights into future Clinical Practice Guidelines recommendations.

**Trial registration:** ClinicalTrials.gov identifier: NCT03980132.

## 1. Background

Graves' disease (GD) is the most common cause of hyperthyroidism. Most patients with GD are initially treated with antithyroid drugs (AT) (thionamides), occasionally followed by surgery or radioactive iodine when failure, intolerance, or relapse after AT treatment [1]. As an alternative to radioiodine, surgical treatment offers important advantages such as a low recurrence rate and a rapid resolution of hyperthyroidism, but its use has been hampered by fear of postoperative complications (hypoparathyroidism, recurrent laryngeal nerve injury, hematoma, surgical site infection, etc.), whose overall incidence rate ranges between 30 and 40%. Despite the initial controversy regarding the surgical technique, some meta-analysis and randomized clinical trials have established near-total/total thyroidectomy (TT) as the technique of choice given that its complication rate is similar to that of more conservative procedures, with a lower recurrence rate [2].

Lugol's solution (LS) was first described in 1829 and is composed by iodine and potassium iodide mixed with distilled water. It has a reddish-brown color, and a characteristic bitter and metallic taste. Its use in the preoperative preparation of patients with GD was proposed by Plummer in 1923 with the aim of achieving euthyroidism before surgery, reducing intraoperative bleeding and preventing the development of a perioperative thyroid storm due to the massive release of thyroid hormones during surgery [3]. However, since the introduction of AT, most patients achieve euthyroidism before surgery. In these cases, the only benefit of LS is a theoretical decrease in surgical complexity due to less intraoperative bleeding caused by a drop in glandular vascularization.

The few clinical trials [4–8] published on this subject only analyze intraoperative outcomes, wherein relationship with postoperative complications is limited by the small sample size of the studies. All these studies published to date are single-center, which further limits their sample size, external validity and makes it difficult to obtain meaningful results. Only one prospective study [9] suggests a lower rate of complications in patients prepared with LS. A recent meta-analysis [10] has not been able to demonstrate any clinical benefit after the administration of LS in euthyroid patients undergoing TT for GD and the authors, even though they emphasize the high heterogeneity of the studies included, call into question the validity of the recommendations of the clinical guidelines.

Currently, both the American Thyroid Association [11] and the European Thyroid Association [1] recommend the use of LS in the preparation of patients undergoing surgery, but their recommendations are based on low-quality evidence. Probably because of this lack of high-quality evidence its use has not been generalized. A recent survey estimates that less than a third of the European endocrine surgery units systematically use it [12].

The LIGRADIS trial (Lugol Iodine in GRAves' Disease Surgery) is the first multicenter randomized controlled clinical trial addressing this topic and intends to provide adequate evidence to support future recommendations on the preoperative preparation with LS in patients undergoing TT for GD.

## 2. Methods/design

### 2.1. Objectives

The primary objective is to analyze whether, in euthyroid patients undergoing TT for GD, no preoperative preparation with LS increases the rate of postoperative complications compared to prepared patients or not.

The secondary objective is to evaluate the influence of preoperative preparation on surgical difficulty, intraoperative blood loss, surgical time, intraoperative neuromonitoring results, postoperative length of stay, hospital readmission rate, permanent complications and adverse events.

### 2.2. Study design

The LIGRADIS trial is a multicenter, randomized trial, blinded for the researchers. Patients will be randomized (1:1) to receiving or not preoperative preparation with LS before TT (Fig. 1). Some 19 specialized Endocrine Surgery Units in Spain are willing to participate.

### 2.3. Study population

Patients who meet all of the following criteria will be eligible:

1. Patients  $\geq 18$  years of age.

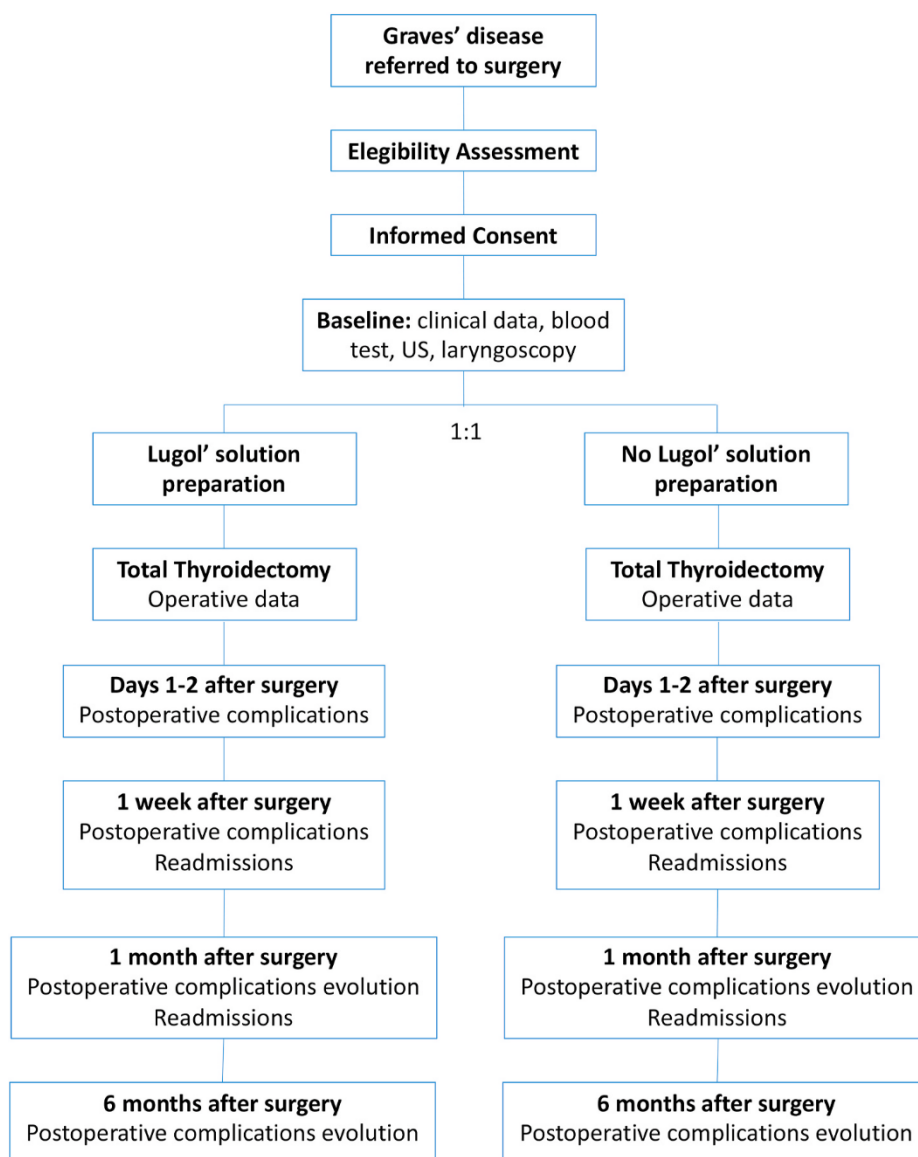


Fig. 1. Flowchart of the LIGRADIS trial.

2. Patients must be able to understand the nature of the study and agree to participate in it, by signing the corresponding informed consent document.
3. GD diagnosis, defined as the existence of hyperthyroidism (TSH values < lower limit of laboratory normality associated with TSI values > upper limit of laboratory normality) that present ultrasonographic data (diffuse vascularization increase) and/or scintigraphy (diffuse uptake of the radioisotope) compatible with GD.
4. Euthyroid state (free T4 and/or free T3 within normal values) at the time of randomization, and under treatment with AT drugs (propylthiouracil, carbimazole or methimazole).
5. Total thyroidectomy planned through a transcervical approach.

Patients will be excluded if they meet any of the following criteria:

1. History of thyroid or parathyroid gland surgery.
2. Concurrent hyperparathyroidism that requires associated parathyroidectomy.

3. Thyroid carcinoma that requires to perform lymph node dissection (central and/or lateral neck compartments) during the same surgical act.
4. Iodine allergy.
5. Consumption of lithium or amiodarone between randomization and administration of LS.
6. Patients classified as category IV according to the American Society of Anesthesiologists (ASA) Physical Status Classification System.
7. Women breastfeeding during the administration of the LS or in the following month.
8. Preoperative vocal cord palsy verified by laryngoscopy.
9. Surgery performed by training specialists or by staff not specifically dedicated to endocrine surgery.
10. Surgery not performed under general anesthesia.
11. Endoscopic, video assisted or remote access surgery.
12. Surgery performed in an outpatient setting.
13. Current illegal drug consumption or alcohol abuse.
14. Participation in any other clinical trial with drugs in the month prior to randomization.

## 2.4. Recruitment procedure

The local investigators will check that the patient meets the eligibility criteria upon diagnosis and confirmation of the surgical indication. Local investigators will explain to the patient the aim of the LIGRADIS trial, the procedure and the potential harms, and will discuss the possibility of being included in it. Patients will be provided with and information sheet and informed consent document. If the patient agrees to participate, the Informed Consent will be signed both by the patient and the investigator. The investigator will provide all the information requested by the patient and allow as much time as needed to decide whether to participate or not. Only when the patient agrees to participate, the randomization will be performed.

## 2.5. Follow-up procedure

After randomization (T2), the next meeting with the patient will be at hospital admission on the day of surgery (T3). Upon arrival, an un-blinded member of the investigator team will assess the assigned group, the presence of adverse events (AE) and, in the LS group, will verify the correct LS intake. This will be the only role of the un-blinded members, and they will not participate in any other evaluation or any further data collection during the study either.

After surgery, follow-up will be programmed according to usual clinical practice. During hospital stay, patients will be evaluated on the first postoperative day (T4) and on the second day (T5) if he was not discharged at day 1. After discharge, patients will be evaluated in an outpatient basis at 1 week (T6), 1 month (T7) and 6 months (T8). T8 visit will be unnecessary if the patient is discharged at T7 in the absence of postoperative complications or if they have been successfully resolved (Table 1).

### 2.5.1. Participants withdrawal

Patients are free to leave the study at any time for any reason, without any consequences. Additionally, the investigator team can withdraw a patient for medical reasons or if there are any concerns about the blinding procedure. Patients' withdrawal and its motivation will be registered.

### 2.5.2. Randomization and blinding

Patients will be randomized to one of the two study groups using a system of centralized allocation, with a 1:1 randomization scheme between treatment arms. Subjects will be assigned by a random number generator performed by a computerized system. This assignment sequence will be hidden from researchers.

For this study, it seems unlikely that the patients' knowledge of the treatment group assigned can influence the measured objectives. Furthermore, due to the organoleptic properties of LS are conferred by the

**Table 1**  
Schedule interventions and assessments of the LIGRADIS trial.

	T1	T2	T3	T4	T5*	T6	T7	T8*
Eligibility screening	X							
Informed consent	X							
Clinical evaluation	X	X	X	X	X*	X	X	X*
Blood test	X			X	X*	X*	X	X*
Cervical ultrasound	X							
Laryngoscopy	X			X*				X*
Allocation		X						
Thyroidectomy			X					
Complications assessment			X	X	X*	X	X	X*

T1 = Baseline; T2 = Allocation; T3 = Intervention; T4 = 1st postoperative day; T5 = 2<sup>o</sup> postoperative day; T6 = 1 week after surgery; T7 = 1 month after surgery; T8 = 6 month after surgery. \* Depending on patients evolution.

presence of iodine in its molecule, it is not feasible to obtain a placebo preparation without iodine with similar properties.

It is very likely that the evaluation of the results could be biased if the surgeon-investigator knows the assigned group. Therefore, our design has been made to keep the surgeon-investigator blinded about the group assigned to each patient. For that purpose, the assignment made in the Hospital Pharmacy Department of each center will be hidden, emphasizing patients on the importance of not revealing to the surgeon whether they are in the LS arm or not, except if the unmasking assumptions apply.

Given the safety profile of the LS, it is unlikely that a medical emergency will occur so as to require urgent unmasking. However, the investigator is authorized to proceed with it if he considers it necessary. If unmasking occurs, the investigator must record the reasons for it, as well as the date and time of the accountable event. The corresponding information will be recorded in the Electronic Case Record Form (ECRF) by the investigator. If it occurs before the second postoperative day, it will be considered a withdrawal criteria.

## 2.6. Trial interventions

Each Hospital Pharmacy Department will prepare the study drug (5% LS) for its outpatient oral administration. This preparation will strictly follow the indications given in the Typified Master Formula provided by the Spanish Drugs and Sanitary Products Agency (AEMPS). Patients assigned to the LS arm will take 5 drops of LS dissolved in water every 8 h, 10 days before surgery. Last dose will be on the night before surgery. The LS will be stored in amber-glass light-resistant containers between 10 and 30 °C.

All surgeries will be performed in reference Endocrine Surgery Units, all of which perform more than 100 thyroidectomies per year. All patients will be attended according to routinely clinical practice of each center. Intraoperative laryngeal nerve monitoring will be done in all cases.

## 2.7. Harms

This study will be stopped if there is any suspicion that patients' health is put at risk because of their participation. The sponsor and the investigators will carry out a continuous safety evaluation of the patients according to Good Clinical Practice defined by the International Conference on Harmonization and current review of the Helsinki Declaration. The sponsor will notify to the accredited Medical Ethical Board any concerns about patients' security without delay.

An AE will be defined as a medical occurrence in a patient participating in the study, regardless of the causal relationship to the treatment assigned. Any AE reported by the patients or those observed by the investigator team will be recorded. Serious AE will be notified to the sponsor within 15 days, except those that are life-threatening or cause the death of the patient, which will be reported without delay. Typical postthyroidectomy complications, defined as the primary outcome, will not be notified unless their severity is above the usual (intensive care unit admission longer than 72 h, life-threatening or death).

## 2.8. Outcomes

### 2.8.1. Primary outcome

The primary outcome will be the development of at least one postoperative complication: hypoparathyroidism, inferior laryngeal nerve injury, postoperative hematoma, surgical site infection or postoperative death.

Hypoparathyroidism is defined by an albumin or protein corrected serum calcium <8 mg/dL the morning after surgery or the need for calcium or vitamin D supplementation between surgery and this determination. Biochemical tests will be performed systematically the morning

after surgery, including at least total serum calcium, total proteins or albumin, and PTH levels.

Inferior laryngeal nerve injury is defined by a vocal cord palsy (uni or bilateral) confirmed by laryngoscopy after surgery. Laryngoscopy will be performed in the first postoperative week when laryngeal nerve injury is suspected due to dysphonia or loss of signal during intraoperative nerve monitoring.

Postoperative hematoma will be considered only when surgical drainage is required.

Surgical site infection will be defined by the presence of any of the following criteria: purulent drainage from the surgical wound, isolation of pathogenic microorganisms in a culture obtained aseptically from the surgical incision, signs or symptoms of infection (local pain, warmth and/or erythema) associated with a positive surgical wound culture or diagnosis of SSI at the discretion of the surgical team.

Postoperative hematoma, surgical site infection and death will be evaluated until 30 days after surgery.

### 2.8.2. Secondary outcomes

Surgical difficulty will be intraoperatively evaluated by the Thyroidectomy Difficulty Scale [13]. Hemorrhage during the procedure will be calculated weighting the gauzes employed and measuring the surgical field liquid aspirated. Regarding nerve monitoring, intraoperative loss of signal will be defined as a vagus signal  $<100\mu\text{V}$  at the end of surgery, provided that the initial vagus signal (previous to recurrent laryngeal nerve dissection) was  $\geq 100\mu\text{V}$ . If it happens, additional information on its characteristics will be recorded (partial/global, side, permanent/temporary, time to recovery if temporary, and probable etiology). Surgical time will be defined as time between skin incision and closure.

Postoperative length of stay and hospital readmissions to treat postoperative complications until postoperative day 30 will be recorded.

Hypoparathyroidism or vocal cord palsy will be considered permanent postoperative complications if they are still unresolved 6 months after surgery. Hypoparathyroidism resolution will be defined as a PTH value above the lower reference laboratory limit and the absence of calcium or vitamin D supplementation to control hypocalcemic symptoms. Vocal cord palsy recovery must be confirmed by laryngoscopy.

## 2.9. Data collection and processing

All the trial variables will be consigned by the investigator in an ECRF.

The investigators will collect the data directly from interviews with participants or from electronic patient files and reports or clinical test results.

## 2.10. Funding source

This project is funded by the Spanish Association of Surgeons by a competitive grant for multicenter studies. This Association has no influence on any part of the design, data collection, analysis or interpretation of the results, all of which will be carried out by the main investigators (JLMN and JMVM).

## 2.11. Statistical analysis

The qualitative variables will be presented by frequencies and proportions. For the comparison of qualitative variables, Pearson's chi-square test or Fisher's exact test will be used as appropriate. The quantitative variables will be presented by the mean  $\pm$  the standard deviation. The normal distribution of quantitative variables will be assessed with the Shapiro-Wilk test and the equality of variances with the Levene's test. For quantitative variables, unpaired Student's t or the Mann-Whitney U tests will be used when applicable, for bivariate analysis.

The estimation of the effect between both treatment groups will be carried out by calculating the relative risk (RR) and its 95% confidence interval. Univariate and multivariate logistic regression models adjusted for confounding variables will be performed. The goodness of fit of the regression formula will be measured by the Hosmer-Lemeshow statistic. The correct classification percentage will also be calculated for the model. In all cases, the construction of the models will be done taking into account the parsimony principle to include a limited number of variables, although the main independent variable and the relevant ones will always be included.

The statistical significance was set at  $p < 0.05$  with bilateral contrast hypothesis for all tests. A sequential evaluation procedure of secondary outcomes will be used.

## 2.12. Sample size

Based on the limited data published on this subject, we estimate that 40% of patients undergoing a TT without preparation with LS could have at least one postoperative complication, while this proportion could drop down to 20% with preparation. As the main outcome will be measured in the early postoperative period, losses in this period are not likely to occur. Assuming an alpha error of 0.05 to find differences among the two groups and a beta error of 0.05 to detect its absence, and using a two-sided  $\chi^2$  test for two independent samples, minimum of 133 patients in each arm will be needed. Therefore, the sample size that has been deemed necessary to recruit is 135 patients in each arm, 270 in total.

## 2.13. Data management and protection

Each participant will receive a unique alphanumeric code composed by three letters that identify the center, and three numbers, consecutively assigned, that identify the patient. Only the investigator team, monitors, health care authorities and regulatory organisms will be able to correlate the patients' identity with the code. Every local investigator will store, in the master file of the study, all the data, which will be kept for 25 years once the study is finished.

All details about the patients' participation will be treated according to data protection regulation.

### 2.13.1. Data safety monitoring

Study monitoring will be performed independently by the Clinical Trials Unit of La Princesa University Hospital. It will include the verification of informed consent signature, the eligibility criteria, the authentication of the data collected in the ECRF and the AE monitoring.

### 2.13.2. Auditing of the participating medical centers

All the centers will receive a remote initiation visit, followed by remote monitoring based on the ECRF collected data, that will be audited by an encoded patient reporting form submitted to the monitors by the investigators. Additionally, there will be monitoring visits after the inclusion of the 3rd, 7th, 11th and 15th patients. These visits could be on-site or remote depending on the situation derived by the COVID-19 outbreak, but at least one will be on-site. Close-out visit will be also on-site.

## 2.14. Ethical approval

The study has been approved by the Institutional Review Board and Ethics Committee of the La Princesa University Hospital (registration code 2018-3750) and conforms in accordance with the provisions of the Helsinki Declaration as revised in 2013 and the confidentiality provided under the current Spanish State and European laws.

### 3. Discussion

To our knowledge, the LIGRADIS trial is the first multicenter randomized trial to evaluate the effect on postoperative complications of the preoperative preparation with LS before TT in euthyroid patients with GD.

The specific organoleptic features conferred by iodine content to the LS makes almost impossible to get a placebo with similar characteristics. Additionally, the primary outcome is defined by the development of postoperative complications that could hardly be influenced by the patient. For these reasons, we believe that the lack of placebo control will have minor consequences in the study conclusions.

When calculating the sample size, we decided to rise the study power to 95%, even if more patients will need to be recruited, in order to achieve enough power to accept our results in case of not founding differences between both groups. In order to reach this number, a multicenter design seems necessary, which will also be important to the external validity of the trial.

#### Availability of the protocol

The full protocol can be obtained from:

- ClinicalTrials.gov: <https://www.clinicaltrials.gov/ct2/show/NCT03980132?term=NCT03980132&draw=2&rank=1>
- Spanish Clinical Trials Registry: <https://reec.aemps.es/reec/estudio/2019-001237-14>

#### Trial status

Finally, the COVID-19 outbreak has affected the normal study development from the beginning. Soon after recruitment began, the LIGRADIS trial was almost stopped. Although recruitment process has been resumed in all participating centers, the epidemiological situation makes this process very slow. We believe that most of the patients that have not been recruited because of COVID-19 outbreak are still potential participants of the study, but it is difficult to predict the global impact of the pandemic on the study. Given these circumstances, we estimate that the follow-up of the patients recruited will be completed by the end of 2022. After analyzing the collected data, these could be published in the second quarter of 2023.

#### Contributors

JLMN, GFA, AVA and JMVM drafted the manuscript. JLMN, GFA, GPMD, MEFR, EPS, ESM, CMN and JMVM made substantial contribu-

tions to the conception and design of this study. All other authors participated in the design of the study and are local investigators at the participating centers. All authors read and approved this manuscript.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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