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Original research

The effect of preoperative Lugol's iodine on intraoperative bleeding in patients with hyperthyroidism

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HIGHLIGHTS

- Preoperative Lugol solution treatment decreased the rate of blood flow, and intraoperative blood loss during thyroidectomy.
- Preoperative Lugol solution treatment was found to be a significant independent determinant of intraoperative blood loss.
- The reduction of intraoperative bleeding allows better visualization and preservation of the surrounding nerves, vasculature, and parathyroid glands.

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ABSTRACT

Aim: To investigate the effect of preoperative Lugol's iodine on intraoperative bleeding in patients with hyperthyroidism.

Material and methods: This controlled, randomized, prospective cohort was carried out on 40 patients who admitted for surgery due to hyperthyroidism. Cases were randomly assigned to receive either preoperative treatment with Lugol solution (**Group 1**) or no preoperative treatment with Lugol solution (**Group 2**). **Group 3** (n = 10) consisted of healthy adults with no known history and signs of hyperthyroidism. Blood flow through the thyroid arteries of patients was measured by color flow Doppler ultrasonography. Free T3, free T4, TSH, thyroid volume and the resistance index of the four main thyroid arteries were measured in all patients.

Results: There was not a significant difference between gender, preoperative serum thyroid hormone levels, or thyroid gland volumes between groups 1 and 2. The mean blood flow of the patients in Group 1 was significantly lower than values in Group 2. When age, gender, thyroid hormone, TSH, thyroid volume, blood flow, and Lugol solution treatment were included as independent variables, Lugol solution treatment (OR, 7.40; 95% CI, 1.02–58.46; $p = 0.001$) was found to be the only significant independent determinant of intraoperative blood loss. Lugol solution treatment resulted in a 7.40-fold decrease in the rate of intraoperative blood loss.

Conclusion: Preoperative Lugol solution treatment was found to be a significant independent determinant of intraoperative blood loss. Moreover, preoperative Lugol solution treatment decreased the rate of blood flow, and intraoperative blood loss during thyroidectomy.

1. Introduction

Hyperthyroidism is related with hemodynamic variations, including increased heart rate and cardiac contractility, and decreased peripheral resistance due to serum thyroid hormone excess [1]. Preoperative preparation of the patient is crucial to avoid intraoperative or postoperative complications and to decrease the vascularity of the gland [2]. The incidence of complications is low in experienced hands; however, a small amount of intraoperative bleeding can reduce the visualization and preservation of the surrounding nerves, vasculature, and parathyroid glands.

Color Doppler examination has become an established imaging technique for assessing thyroid gland vascularity. Several studies revealed that thyroid vascularity has been increased in patients with hyperthyroidism [3]. Hodgson et al. reported that thyroid arterial blood flow correlated remarkably with the levels of free T3, whereas Bogazzi et al. did not find a correlation between Doppler

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findings and serum thyroid hormone levels [4,5].

Lugol solution (inorganic iodide) has been given preoperatively to patients to limit intraoperative bleeding and related complications resulting from thyroid gland vascularization [6]. It is commonly used in the preparation of patients for thyroidectomy [7]. This effect transiently blocks thyroid hormone generation, with thyroid hormone synthesis recovering in a few days or weeks. Although the practice has widespread use, there is still no agreement on its effectiveness. The main reason for this lack of consensus stems from the variety of treatment protocols in terms of drug dosage and concurrent management of antithyroid therapy [8]. Most studies related to the effects of Lugol solution are based on indirect evaluations, such as the impression of the surgeon [9].

The aim of the present study was to investigate the effect of preoperative Lugol's iodine on intraoperative bleeding in patients with hyperthyroidism.

2. Materials & methods

2.1. Study design

This randomized, controlled, prospective cohort has been performed in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board. Written informed consent was obtained from all subjects.

Initially, a total of 48 patients have admitted to the *Department of General Surgery* of our tertiary care center for surgery with the diagnosis of hyperthyroidism. Six patients did not meet the inclusion criteria whereas two patients declined to participate in the current study. Forty patients (Graves' disease or multinodular goiter) were considered as eligible for the study. A parallel trial design was applied and allocation ratio for Groups 1, 2 and 3 were 2:2:1.

All patients were treated with antithyroid drugs until they were euthyroid. Subsequent to randomisation, the patients received either Lugol's iodine, 0.8 mg/kg for 10 days (**Group 1**, $n = 20$), or did not receive Lugol's iodine (**Group 2**, $n = 20$). The patients in Group 1 immediately underwent surgery after treatment with Lugol's iodine for 10 days. Antithyroid drugs were continued throughout the study. **Group 3** ($n = 10$) consisted of healthy adults with no known history and signs of hyperthyroidism.

Exclusion criteria consisted of a solitary toxic nodule, fine-needle aspiration biopsy result indicating cancer or suspicious cytology, anticoagulant usage, a previous thyroid operation, pregnancy and refusal to participate in this study. Follow-up and management of patients was made in collaboration with radiology and endocrinology departments of our institution.

2.2. Surgical procedure

In all patients, indirect laryngoscopic examination was used to evaluate vocal cord motility before and after surgery. Total thyroidectomies were performed by the same surgeon in all patients. The duration of surgery, the volume of blood loss measured as the amount of blood in the suction bottle were recorded for each patient.

Persistent nerve palsy was defined as persistent dysfunction and clinical dysphonia that lasted for 6 months postoperatively. Hypocalcemia was defined as a serum calcium level less than 8 mg/dl after the operation. Persistent hypoparathyroidism was defined as serum PTH levels less than 10 pg/ml in patients that need treatment for longer than 3 months to achieve and maintain normocalcemia.

2.2.1. Primary and secondary outcome measures

Thyroid volume, thyroid glandular blood flow features and thyroid hormone levels were the main parameters investigated in this trial.

2.3. Doppler ultrasonography

Color flow Doppler ultrasonography using a high frequency wideband linear transducer (frequency range, 7.3–11.4 MHz) was performed before treatment of Group 1 patients with Lugol solution. Vascular studies were implemented routinely 24 h before surgery. Ten healthy medical staff volunteers were included as healthy controls (**Group 3**). The same investigator who was unaware of the laboratory values at the time of the examination performed each color Doppler examination blindly.

Thyroid volume was measured by ultrasound and calculated using the ellipsoid model (width x length x thickness x 0.5233 for each lobe) [10]. The superior and inferior thyroid arteries on each side of the neck were initially identified, followed by peak systolic and diastolic velocities, vessel diameter, and the flow volumes were calculated using measurement tools installed within the Doppler unit. The study evaluated the resistance index (RI) of the four main thyroid arteries, sampled near their entrance into the gland. The RI was evaluated according to the following formula: (peak systolic velocity/end diastolic velocity)/peak systolic velocity [11,12]. A mean thyroid RI and blood flow rate were calculated from 12 measurements, with four for each artery.

2.4. Biochemical analysis

Normal ranges of the parameters under investigation were as follows: free T3 (FT3), 2.3–4.2 pg/mL; free T4 (FT4), 0.74–1.52 ng/dL; TSH, 0.35–5.50 uIU/liter.

No changes have been made to trial outcomes after the trial commenced. The sample size was determined on the basis of inclusion of all volunteer patients diagnosed in the study period. Random allocation sequence was provided using a computer program. Any restriction such as blocking was not performed. Determination of the random allocation sequence, enrolment of participants and assignment of participants for interventions were made by the primary investigator (YY). Care providers and participants were blinded to interventions.

2.5. Statistical analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v21 (*SPSS Inc*., *Chicago*, *IL*, *USA*). A normal distribution of the quantitative data was checked using Kolmogorov-Smirnov test. Parametric tests (Students t and chi-square tests) were applied to data of normal distribution and non-parametric tests (Mann–Whiney U test) were applied to data of questionably normal distribution. Logistic regression was performed to find the risk factors (age gender, FT4, TSH, lugol's solution use, thyroid volume, blood flow) for intraoperative bleeding. Correlations between continuous variables were determined nonparametrically using Spearman's rho. Continuous data were presented as mean ± standard deviation. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

3. Results

Fig. 1 demonstrates the flow chart of the present study and the current study was performed. Baseline descriptive, clinical and radiological characteristics of study groups are presented in Table 1. The mean age of the whole study group was 43.97 ± 9.25 (range, 25–63) years. The female/male ratio was 31:9. The mean serum FT3, FT4, and TSH levels were 2.89 ± 0.62 pg/mL, 1.04 ± 0.37 ng/dL,

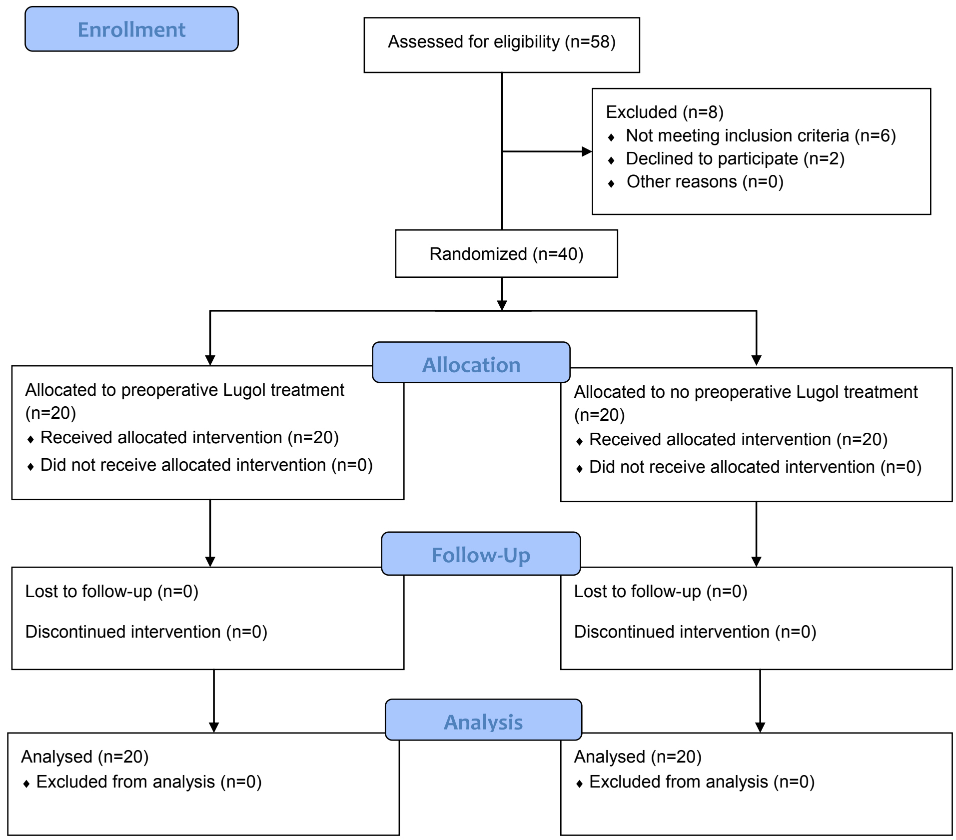

Fig. 1. Consort 2010 flow diagram for the present study.

Table 1
Clinical and laboratory parameters according to groups 1 and 2.

	Group 1 (n = 20)	Group 2 (n = 20)	*p* Value
Age (years)	38.69 ± 81.71 (range, 25–56)	47.25 ± 8.72 (range, 29–63)	0.030
Gender (female/male)	16/4	16/4	1.000
FT3 (pg/mL)	3.16 ± 0.65	3.06 ± 0.60	0.693
FT4 (ng/dL)	0.99 ± 0.23	1.08 ± 0.47	0.779
TSH (uIU/mL)	0.67 ± 0.55	0.80 ± 0.94	0.529
Thyroid gland volume (ml)	70.98 ± 16.35	69.80 ± 19.60	0.925
Intraoperative blood loss (ml)	76.15 ± 27.03	172.20 ± 96.27	0.0001

and 0.74 ± 0.76 uIU/mL, respectively. The mean thyroid gland volume, blood flow, RI, and intraoperative blood loss were 70.52 ± 18.04 mL, 78.65 ± 69.62 mL/dk, 0.77 ± 1.09%, and 124.17 ± 85.07 mL, respectively. The normal controls consisted of 10 healthy subjects. There was no perioperative mortality. The incidence of transient vocal cord paralysis and hypoparathyroidism were 2.5 and 2.5%, respectively. Persistent vocal cord paralysis and hypoparathyroidism were not encountered in our series.

The mean ages were 38.69 ± 81.71 (range, 25–56) years in *Group 1 (n = 20)* and 47.25 ± 8.72 (range, 29–63) years in *Group 2 (n = 20)* ($p = 0.030$). The female/male ratios were 16:4 in both groups. There was not a significant difference between gender, preoperative serum thyroid hormone levels, or thyroid gland volumes between Groups 1 and 2 (Table 1).

The mean blood flow and RI of the control group (*Group 3*) (n = 10) were 21.32 ± 8.06 ml/min and 0.62 ± 0.09%, respectively. The mean blood flow of the patients in Group 1 was significantly lower than values in Group 2 58.61 ± 49.27 vs. 98.69 ± 81.71 ml/min; ($p \leq 0.05$). These values were higher than the values of control subjects. No significant difference was observed for mean RI of the patients between Group 1 and Group 2 (0.75 ± 1.09 vs. 0.77 ± 1.09%; $p = 0.398$). These values were higher than the values of control subjects (Table 2).

Stepwise regression analysis: When age, gender, thyroid hormone, TSH, thyroid volume, blood flow, and Lugol solution treatment were included as independent variables, Lugol solution treatment (OR, 7.40; 95% CI, 1.02–58.46; $p = 0.001$) was found to be the only significant independent determinant of intraoperative blood loss. Lugol solution treatment resulted in a 7.40-fold decrease in the rate of intraoperative blood loss.

No harms, hazardous or unintended outcomes were observed in any participants during the trial.

4. Discussion

The main aim of our study was to investigate the effect of Lugol solution on vascular density in hyperthyroidism, and we found that Lugol solution treatment before surgery is significantly associated with thyroid vascularity and intraoperative blood loss. According to logistic regression analysis, Lugol solution treatment before surgery

Table 2
Doppler ultrasonography parameters according to groups 1, 2, and 3.

	Group 1 (Lugol +) (n = 20)	Group 2 (Lugol−) (n = 20)	Group 3 (Control Group) (n = 10)	*p* Value
Blood flow (ml/min)	58.61 ± 49.27	98.69 ± 81.71	21.32 ± 8.06	Group 1*vs*2 = 0.043 Group 1vs3 = 0.241 Group 2vs3 = 0.324
Resistance index (%)	0.75 ± 1.09	0.77 ± 1.09	0.62 ± 0.09	Group 1*vs*2 = 0.398 Group 1vs3 = 0.423 Group 2vs3 = 0.448

was the only significant independent determinant of intraoperative blood loss.

Doppler techniques seem to be the best methods to evaluate the characteristics of blood flow within the intraparenchymal vessels of the thyroid gland, being a direct noninvasive method without the drawbacks of ionizing radiation and of intraoperative placement of electromagnetic flowmeters [13,14]. Higher intrathyroidal blood flow and increased peak systolic velocity have been documented in hyperthyroidism [14,15]. In the present study, the blood flow of thyroid arteries was higher than the values obtained in control subjects. Ansaldo et al. aimed to evaluate the effects of Lugol solution therapy in a series of patients with hyperthyroidism through analysis of the RI of thyroid arteries [9]. After Lugol solution treatment, RI reached a mean value similar to that of the normal subjects. RI is a semiquantitative, easy-to-obtain, and reproducible measurement reflecting the vascular impedance within the vascular bed distal to the site of sampling. Changes in vascular impedance after drug administration have been widely studied using this method. Although surgeons administer Lugol solution to decrease thyroid gland vascularity, there is still not an agreement on its effectiveness [16]. Because studies are mostly based on empirical or indirect evaluations, such as the impression of the surgeon, objective results of the effects of Lugol solution on the gland are difficult to achieve [17]. Chang et al. demonstrated a reduction of blood volume flow within the superior thyroid arteries after Lugol solution treatment in patients with Graves' hyperthyroidism [18]. In the present study, Lugol solution treatment resulted in a significant decrease of the mean basal blood flow in patients with hyperthyroidism.

There is no consensus in literature on the amount of iodo-iodide solution needed to obtain reduction in glandular friability and blood loss during operation. In our series, we used the dose of 0.8 mg/kg of iodine (given in 10 days); this dose is lower than others reported in literature [19,20]. A study documenting the response of DTG glands to different doses of Lugol's solution could provide information about the best therapeutic regimen for this purpose.

The incidence of life-threatening bleeding after thyroidectomy has been reported as 0.25–2.3% in the literature [21]. An enlarging hematoma compressing airways is an indication for emergency exploration. It usually emerges within the first postoperative 24 h [22]. The most important factor in the prevention of such a bleeding involves meticulous and attentive surgery and achievement of good hemostasis. In the literature, it has been reported that development of bleeding is not related to the amount of resection, but it is associated with hemostasis and meticulous surgical technique [21]. In the present study, any incident of life-threatening bleeding was not seen.

As a result of the cases with unilateral damage of the recurrent laryngeal nerve (RLN) hoarseness develops, while bilateral RLN damage causes serious airway obstruction [23]. Hoarseness as a result of RLN damage lasting for more than a year is termed as permanent hoarseness. Cases with hoarseness which improve up to one year after RLN damage where indirect laryngoscopy demonstrates improvement in vocal cord paralysis, are called cases with transient RLN damage In the literature the incidence of permanent and transient RLN damage after thyroidectomy has been reported as 0.1–3.2 and 2–8%, respectively. In the present study, permanent and transient RLN damage were seen in 0 and 0.2% of the cases, respectively [24].

Permanent hypocalcemia occurs as a result of removal of parathyroid glands or devascularization. Hypocalcemia cured up to postoperative first year is accepted as transient hypocalcemia [25]. In the present study, permanent and transient hypocalcemia after total thyroidectomy were seen in 0% and 2.1% of the patients, respectively.

The main limitation of our study was the small sample size which may cause a high probability of a type 1 error. Second limitation is the experience restricted to the outcomes of a single institution. Third, some details of history and factors that may influence the outcome may not be completely documented. Due to these restrictions, associations should be interpreted with caution.

In conclusion, preoperative Lugol solution treatment was found to be a significant independent determinant of intraoperative blood loss. Moreover, preoperative Lugol solution treatment decreased the rate of blood flow, and intraoperative blood loss during thyroidectomy. The reduction of intraoperative bleeding allows better visualization and preservation of the surrounding nerves, vasculature, and parathyroid glands.

Ethical approval

The study was approved by the hospital's ethics committee and all of the patients were informed (Reference number: 2010/179).

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Author contribution

Yeliz Yilmaz → Designed the study, work the manuscript.
Kemal Erdinc Kamer → Participated in study design.
Erdem Sari → Participated in data collection.
Turan Acar → Performed the statistical analysis.
Orhan Ureyen → Participated in data collection.
Onder Karahalli → Participated in data collection.

Conflicts of interest

The authors declared no conflicts of interest with respect to the authorship and /or publication of this article.

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