Clinical Thyroidology / Review

European
Thyroid Journal

Eur Thyroid J 2017;6:20–25
DOI: 10.1159/000450976

Received: May 24, 2016
Accepted after revision: September 21, 2016
Published online: November 22, 2016

Pre-Operative Lugol's Iodine Treatment in the Management of Patients Undergoing Thyroidectomy for Graves' Disease: A Review of the Literature

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Key Words
Graves' disease · Iodine · Thyroid function · Total thyroidectomy · Guidelines

Abstract
Objective: To undertake a review of the relevant English literature published on the pre-operative use of Lugol's iodine in the management of patients undergoing thyroidectomy for Graves' disease. ***Search Strategy:*** We reviewed all relevant papers found through Ovid Medline, PubMed, EMBASE and the American Thyroid Association website. Searches were limited to the English language only. ***Evaluation Method:*** The critical appraisal tool CASP was used to help analyse the papers. Following this, the evidence was ranked using the Harbour and Miller classification of hierarchy. ***Results:*** Four papers were deemed appropriate for analysis. The evidence contained within the review is considered weak. The literature available in the public domain regarding the use of iodinated solutions in the pre-operative period for those patients about to undergo thyroidectomy for Graves' disease is scant. ***Conclusion:*** Having undertaken an extensive literature review, we are of the opinion that the evidence on which the American Thyroid Association's guidance on the use of preoperative Lugol's iodine is based is tenuous. There appears to be little in the way of sound clinical evidence that post-operative outcomes are any different following a course of Lugol's iodine. Given the lack of robust clinical evidence regarding the clinical need for iodine solution in the pre-operative period, it appears clear that a larger, prospective, randomised controlled trial of all relevant outcomes – clinical and scientific – is required to answer whether or not patient preparation with Lugol's iodine is in fact necessary prior to operative intervention for Graves' disease.

Introduction

Thyrotoxicosis is a relatively common endocrine disease with an annual incidence of approximately 1 in 2,000 in Europe [1]. The most common cause of an overactive thyroid gland is the autoimmune condition Graves' disease. Although medical treatments exist for Graves' disease, surgical excision of the thyroid gland via total thyroidectomy offers a definitive treatment. Patients undergoing thyroidectomy to treat Graves' disease are frequently treated with Lugol's iodine (also known as potassium iodide) in the days preceding their operation [2].

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Traditionally, Lugol's solution is taken orally at a dose of 0.5 ml 3 times daily, but clinical practice varies widely [3]. The practice was established in the 1920s following a reduction in peri- and post-operative mortality when using Lugol's iodine [4, 5]. Since then, the medical management of hyperthyroid patients has advanced considerably, such that patients are now often treated pre-operatively with beta-blockers and thiouracil-containing medications [4].

The American Thyroid Association (ATA) states in their guidelines on the management of hyperthyroidism that 'Whenever possible, patients undergoing thyroidectomy should be rendered euthyroid with methimazole, and potassium iodide should be given in the immediate preoperative period'. Also highlighted within the guidelines are circumstances where it is not possible to render the patient euthyroid and that there is a need for urgent thyroidectomy. Similarly, guidance exists for when the patient is allergic to anti-thyroid medications. In these instances 'the patient should be adequately treated with beta-blockade and potassium iodide in the immediate preoperative period' [6]. The aim of this is to reduce the vascularity of the thyroid gland immediately prior to surgery and therefore reduce blood loss and improve visualisation of important structures intraoperatively [7, 8]. It has also been shown to reduce the risk of intra- and post-operative thyrotoxic storm [9], in addition to acutely inhibiting hormonal secretions [10] and the organification of iodine within the thyroid gland [11]. It is likely that these factors have influenced the use of Lugol's iodine over the years in this setting.

The aim of this review is to evaluate the evidence underpinning the use of Lugol's iodine solution in the preparation of patients due to undergo thyroidectomy for Graves' disease, and to assess its impact on clinical outcome.

Search Strategy

Ovid Medline, PubMed and the ATA website were used to help identify relevant publications that have aided the answering of this question. Searches were limited to the English language only. References contained within articles have also been evaluated to determine their potential suitability with regard to the question. Although a potentially divisive topic, the literature in the English language is limited to only a handful of current articles. It was therefore necessary to extend the search term beyond 5 years to ensure that a comprehensive analysis of the literature was undertaken. Only those papers that evaluated the use of iodinated solutions in the pre-operative management of patients undergoing thyroidectomy were evaluated. Following review of the abstracts, 4 papers were deemed appropriate for analysis. A tabulated form of the search terms used can be found in table 1 and a summary of the pertinent points of included publications appears in table 2. Following analysis, the evidence was ranked using the Harbour and Miller [12] classification of hierarchy.

Table 1. List of search terms

	Search term	Number of publications
1	Thyroidectomy/	17,751
2	Graves' disease/	13,479
3	Lugol's iodine	194
4	Potassium iodide/	1,772
5	1 and 2	1,230
6	3 or 4	1,966
7	5 and 6	13

Analysis of the Literature

Shinall et al. [2] performed a retrospective case-note analysis of patients undergoing total thyroidectomy. The 2 groups of patients under study were those who had a diagnosis of Graves' disease and those diagnosed with toxic multi-nodular goitre (TMNG). By comparing these 2 groups, the authors have attempted to show that there is no difference in outcome when looking at a group that is never treated with iodine versus a group for which iodine treatment has been recommended. The authors identified 165 patients with Graves' disease over a 5-year period, 3 of whom were excluded because of pre-operative iodine therapy, and 102 patients with TMNG.

Firstly, the authors address a specific question. Are there any differences in post-operative outcome following total thyroidectomy in patients who have Graves' disease who do not receive preoperative iodine treatment and in those who undergo total thyroidectomy for a TMNG? Shinall et al. [2] have clearly defined the cases and comparison group. There does not appear to have been a power calculation in this particular study, increasing the likelihood of a type II error; however, they performed statistical analysis using Student's t test, the χ^2 test and multivariate analysis. The outcomes of thyroidectomy were considered in controls with a similar pathology

Table 2. Summary of publications reviewed

First author [ref.]	Year	Comparison	Main findings	Level of evidence
Shinall [2]	2013	TMNG versus Graves' disease thyroidectomy outcomes not treated with Lugol's iodine	No significant difference in blood loss between the TMNG and Graves' patients not treated with Lugol's iodine who underwent thyroidectomy	2–
Santosh [4]	2014	Outcomes in all patients undergoing thyroidectomy not treated with Lugol's iodine	No difference in post-operative complication rates in patients not given Lugol's iodine	2–
Yabuta [13]	2009	Graves' patients treated with Lugol's iodine versus those not treated with Lugol's iodine	No difference in intra-operative blood loss between patients treated with Lugol's iodine and those not treated	2–
Erbil [8]	2007	Graves' patients treated with Lugol's iodine versus those not treated with Lugol's iodine	Microvessel density and intra-operative blood loss was significantly lower in patients treated with Lugol's iodine	1–

but, importantly, not the same pathology. The exposure of the cases and controls is well-documented and easy to follow, in that none of those who were included received any pre-operative iodine therapy. The demographics of the population studied are broadly comparable, thereby minimising the risk that any findings were due to a fundamental difference between the 2 groups. Regarding post-operative outcomes, it is important to note that there was no statistical difference ($p < 0.05$ was significant) between the 2 groups with regard to blood loss. This is deemed to be an important clinical indicator as it reflects on a cleaner surgical field, and is argued by advocates of iodinated solutions to be a major reason to treat patients pre-operatively with iodine. It must be kept in mind that the data in this study was collected retrospectively and this almost certainly introduces bias. There was no randomisation or blinding within this retrospective study and there is no comment as to whether patients were assigned to 1 surgeon or a group of surgeons, raising the potential for selection bias. Additionally, there is no mention of how blood loss was quantified; given that this is one of the most important clinical parameters under study, it is imperative to know this information.

The only statistically significant difference in post-operative outcome identified was that those with TMNG suffered from post-operative transient hypocalcaemia more frequently. There was no difference in recurrent laryngeal nerve palsy, post-operative haematoma or length of hospital stay. The authors made allowances for the fact that age and BMI displayed statistically significant differences between the 2 groups, and they utilised multiple linear regression analysis to minimise confounding. Although it is hard to draw firm conclusions from this study, it does offer an alternative view on the necessity of pre-operative iodine. As the publication was a case-control study with a significant risk of bias, it ranks as a level 2– piece of evidence according to the 2001 classification of Harbour and Miller [12].

Santosh and Karanam [4] retrospectively analysed operative outcome data from 105 patients undergoing thyroid surgery. Strict exclusion criteria were identified including which patients were on anti-coagulants or who had had previous thyroid surgery, thereby attempting to control for potential confounding factors. The study focus is clear that none of the patients undergoing surgery in this study received pre-operative Lugol's iodine. The same surgeon operated on all patients. Two patients required treatment for post-operative hypocalcaemia and 1 sustained recurrent laryngeal nerve injury that persisted beyond 6 months (0.9%). The authors' conclusion is that there does not appear to be any convincing evidence of the advantages of pre-operative preparation of patients with Lugol's iodine.

There are numerous critical points to make regarding this publication. The study population is not clearly identified. Basic demographic data is not included; the age, sex and ASA grade of the patients is not available for comparison, and so we do not know if there was a fundamental difference between the 2 groups. Although major complications such as nerve injury and hypocalcaemia are evaluated, there is no mention of operative time, blood loss or wound infection and seroma rates. These

issues are particularly relevant to the study question and again relate to the main argument that pre-operative treatment with iodine reduces thyroid vascularity. Clear criteria for the identification of nerve injury and hypocalcaemia were used. The exclusion criteria were explicitly stated, but there is no mention of the actual numbers excluded, or if a full data set was obtained for each patient that was included. The breakdown of diagnoses for patients is not given, which one would assume is particularly pertinent when addressing the need for Lugol's iodine in patients with Graves' disease who are about to undergo thyroidectomy. Although it is mentioned that all patients were clinically euthyroid, there is no further information as to whether this was physiological or was brought about by medical intervention. There is no mention of statistical analysis – if any – of the data presented. A comparison is made between this paper and the post-operative outcome rates determined by other studies, which are broadly comparable with this publication. However, many facets, as already explained, have been overlooked. Although at first reading the conclusion appears to make sense, there is, in fact, very little justification given based on the evidence provided. Bias was likely introduced throughout this publication. As in the previous article, there was no randomisation, blinding or power calculation to help reduce type II errors. This second article is also considered a level 2– piece of evidence as it is a retrospectively collected dataset of cases and controls.

An interesting retrospective article by Yabuta et al. [13] looked at the difference in volume of thyroid tissue in patients undergoing thyroidectomy for Graves' disease. The 2 groups were those who received potassium iodide solution pre-operatively and those who did not. The study population is clearly identified as patients undergoing thyroidectomy for Graves' disease between 2006 and 2008. Clearly defined exclusion criteria have been applied, again helping to minimise confounding factors. All patients with dual thyroid pathology or who had not undergone ultrasound scan within the previous 6 months were excluded, as were those who received potassium iodide for >1 month. Furthermore, those with a thyroid >200 cm^3 were excluded as it was felt that, beyond this, the reliability of measurement was impeded. This left a study population of 113 patients. It is not possible to comment on whether this is an appropriate number as no power calculations were discussed. All patients received anti-thyroid medications. There was no randomisation of potassium iodide therapy and the decision to treat with potassium iodide was left to the operating surgeon. This is potentially a source for selection bias. In addition, there was no standardised dose of potassium iodide administered and the dose varied according to surgeon preference and TSH level. The controls in this study were therefore patients undergoing thyroidectomy for Graves' disease for whom the only treatment had been anti-thyroid medications (total n = 24). Thyroid volumes were measured at least once within 6 months pre-operatively and again within 3 days prior to surgery. Thyroid volume measurements were made using a specific ultrasound scanning machine and model. Calculations of volumes were made using a specific illustrated method. Statistical tests were appropriate – non-parametric Mann-Whitney U tests and parametric Student's t tests were adopted. The significance level was set at $p < 0.05$.

There were no statistically significant differences in the demographic composition of the 2 treatment groups. There was no significant difference in length of procedure, nor was there any difference in intra-operative blood loss. No mention is made of post-operative complications. This vital omission is arguably the most important indicator of any intervention that is purported to affect surgical outcomes. The volume of thyroid tissue increased significantly in size following the administration of potassium iodide, but there was no significant increase in thyroid volume in patients receiving anti-thyroid drugs only. Whilst evaluating the confidence intervals quoted, one notes they are large and cross the initial volume of thyroid tissue considerably. This may be due to the number of patients recruited to the study. It is also hard to determine whether or not the results obtained are a true representation of the use of potassium iodide. The lack of randomisation and surgeons' 'hand-picking' of cases to receive potassium iodide make it difficult to reach any concrete conclusions. There is no mention within the publication on how refusal to take part in the study was dealt with. For this reason, it would be appropriate for a larger study using a randomisation process to be carried out before any meaningful conclusions can be reached. To this end, this study has an evidence rating level of 2–.

Erbil et al. [8] conducted a randomised controlled trial looking at the effect of pre-operative Lugol's iodine solution on the vascularity of the thyroid gland in Graves' disease. This piece of work clearly outlines the population to be studied. The 36 consecutive patients awaiting surgery for Graves' disease were randomly allocated to either receive 10 days of Lugol's solution pre-operatively or not to receive any. The way in which randomisation was con-

ducted is not iterated within the paper and the blinding of patients is not commented on – a potential source of bias. The inclusion and exclusion criteria were strictly outlined and selected surgeons carried out the operations. The outcomes of the study were clearly defined. Data is presented for all participants enrolled at the start of the study – thereby minimising the effect of attrition bias. All those who started the trial were analysed according to the group to which they were allocated. Microvessel density was assessed using biochemical analysis. Post-operative complications were recorded and were clearly defined for the purposes of the study. The statistical analyses of the groups were clearly outlined, using parametric, non-parametric and correlation calculations to determine significant differences (level set at $p < 0.05$) between the 2 groups.

There were no significant differences in patient demographics between the 2 groups. The primary outcome, microvessel density, was found to be significantly lower in the patients treated with pre-operative Lugol's iodine. Secondary outcomes such as blood flow and blood loss during surgery were also found to be significantly lower in the patients undergoing treatment (a 9.3-fold decrease). The confidence intervals are again understandably large within this study, owing to the small groups under study. No patient suffered from permanent recurrent laryngeal nerve injury or persisting hypocalcaemia. The conclusion drawn is that Lugol's iodine solution decreased the rate of blood flow through the thyroid gland but also reduced the intra-operative blood loss. From this, the authors state that this reduction in vascularity allows for better visualisation and preservation of the surrounding nerves, vessels and parathyroid glands. Whilst this makes sense on paper, the clinical relevance of this should not be overestimated. The authors themselves already identified that there were no untoward complications in either group. This is arguably due to chance in such a small cohort of patients and would need larger studies to confirm that the use of Lugol's iodine was directly related to a reduction in complications. Furthermore, the level of blood loss that the authors allude to is comparatively small (54 ml in those treated with Lugol's iodine and 108 ml in those not treated with it).

As a randomised controlled trial, this paper ranks higher in the Harbour and Miller classification; however, due to the omission of the randomisation process and the lack of clarity regarding the blinding of the intervention, there is potentially a high risk of bias. For this reason, the quality of the evidence must be rated as 1–.

Discussion

The levels of evidence contained within this review are, on the whole, weak. The literature available within the public domain regarding the use of iodinated solutions in the pre-operative period for patients about to undergo thyroidectomy for Graves' disease is scant. As identified whilst critiquing the above literature, the scientific basis for the use of Lugol's iodine may indeed have some merit. Reduced blood flow within the thyroid gland and a reduction in blood loss during the operation itself appear, at least at first, as attractive attributes for any surgeon operating within the head and neck region. On closer analysis of the above literature, however, it would appear that the clinical relevance of such attributes are somewhat lacking. Furthermore, the surgical issues surrounding thyroid storms have not been dealt with. Given that an iatrogenic thyroid storm would have potentially life-threatening consequences, it is important to know the consequences of handling thyroid tissue in patients with known hyperthyroidism at the time of operation. Given that it is well-known that iodine acutely inhibits hormone secretions within a matter of hours following administration, a course of Lugol's iodine in a patient with hyperthyroidism prior to operative intervention will aid in preventing a thyrotoxic storm. This said, in those patients who are euthyroid in the pre-operative phase, it would be reasonable to argue that the benefits from pre-operative Lugol's iodine administration, if any, are due to the effects on thyroid vascularity and the minimisation of blood loss.

None of the papers identify whether or not there were any adverse effects of taking iodine in the pre-operative period. Even more importantly, perhaps, there is no mention of the incidence of adverse outcomes in the hyperthyroid patient for whom surgery was delayed so that the stipulation in the ATA guideline could be met.

Another point to note is the heterogeneity of the groups studied, not only within the individual papers, but also between them. Shinall et al. [2], although attempting to answer a specific question compared thyroidectomy outcomes in patients with Graves' disease and toxic multinodular goitre. Santosh and Karanam [4] similarly try to answer a specific question by looking at post-operative outcomes following thyroid surgery. The indications for those undergoing surgery were numerous. Not only does this greatly reduce the ability to answer the question regarding the need for iodine solution in the pre-operative period for any given condition, it makes a comparison with other trials extremely difficult.

Conclusion

It is our opinion that the evidence behind the ATA guidance on the use of preoperative Lugol's iodine is tenuous. There appears to be little sound clinical evidence that post-operative outcomes are any different following a course of Lugol's iodine. Given the lack of robust clinical evidence regarding the clinical need for iodine solution in the pre-operative period, it appears clear to us that a larger, prospective, randomised controlled trial of all relevant outcomes – clinical and scientific – is required to answer whether or not patient preparation with Lugol's iodine is in fact necessary prior to surgical intervention for Graves' disease.

Disclosure Statement

The authors confirm there are no conflicts of interest to declare.

References

1 Vaidya B, Pearce S: Diagnosis and management of thyrotoxicosis. Br Med J 2014; 349:g5128.
2 Shinall MC Jr, Broome JT, Baker A, Solorzano CC: Is potassium iodide solution necessary before total thyroidectomy for Graves' disease? Ann Surg Onc 2013;20:2964–2967.
3 Farling P: Thyroid disease. Br J Anaesth 2000; 85:15–28.
4 Santosh K, Karanam L: Preoperative preparation with Lugol's iodine in thyroidectomy of euthyroid patients – is it really mandatory? An otorhinolaryngologists view. J Clin Diagn Res 2014;8:KC01–KC02.
5 Coyle PJ, Mitchell JE: Thyroidectomy: is Lugol's iodine necessary? Ann R Coll Surg Engl 1982; 64:334–335.
6 Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, Laurberg P, McDougall IR, Montori VM, Rivkees SA, Ross DS, Sosa JA, Stan MN: Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 2011;21:593–646.
7 Ansaldo GL, Pretolesi F, Varaldo E, Meola C, Minuto M, Borgonovo G, Derchi LE Torre GC: Doppler evaluation of intrathyroid arterial resistances during preoperative treatment with Lugol's iodide solution in patients with diffuse toxic goiter. J Am Coll Surg 2000;191: 607–612.
8 Erbil Y, Ozluk Y, Giris M, Salmaslioglu A, Issever H, Barbaros U, Kapran Y, Ozarmagan S, Tezelman S: Effect of Lugol's solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease. J Clin Endocrinol Metab 2007;92:2182–2189.
9 Carroll R, Matfin G: Endocrine and metabolic emergencies: thyroid storm. Ther Adv Endocrinol Metab 2010;1:139–145
10 Emerson CH, Anderson AJ, Howard WJ, Utiger RD: Serum thyroxine and triiodothyronine concentrations during iodide treatment of hyperthyroidism. J Clin Endocrinol Metab 1975;40:33.
11 Wolff J, Chaikoff IL: The temporary nature of the inhibitory action of excess iodine on organic iodine synthesis in the normal thyroid. Endocrinology 1949;45:504.
12 Harbour R, Miller J: A new system for grading recommendations in evidence-based guidelines. Br Med J 2001;323:334–336.
13 Yabuta T, Ito Y, Hirokawa M, Fukushima M, Inoue H, Tomoda C, Higashiyama T, Kihara M, Uruno T, Takamura Y, Kobayashi K, Miya A, Matsuzuka F, Miyauchi A: Preoperative administration of excess iodide increases thyroid volume of patients with Graves' disease. Endocr J 2009;56:371–375.