Effects of Preoperative Iodine Administration on Thyroidectomy for Hyperthyroidism: A Systematic Review and Meta-analysis

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Abstract

Objective. The current guidelines recommend that potassium iodide be given in the immediate preoperative period for patients with Graves’ disease who are undergoing thyroidectomy. Nonetheless, the evidence behind this recommendation is tenuous. The purpose of this study is to clarify the benefits of preoperative iodine administration from published comparative studies.

Data Sources. We searched PubMed, Embase, Cochrane, and CINAHL from 1980 to June 2018.

Review Methods. Studies were included that compared preoperative iodine administration and no premedication before thyroidectomy. For the meta-analysis, studies were pooled with the random-effects model.

Results. A total of 510 patients were divided into the iodine (n = 223) and control (n = 287) groups from 9 selected studies. Preoperative iodine administration was significantly associated with decreased thyroid vascularity and intraoperative blood loss. Significant heterogeneity was present among studies. We found no significant difference in thyroid volume or operative time. Furthermore, the meta-analysis showed no difference in the risk of postoperative complications, including vocal cord palsy, hypoparathyroidism/hypocalcemia, and hemorrhage or hematoma after thyroidectomy.

Conclusion. Preoperative iodine administration decreases thyroid vascularity and intraoperative blood loss. Nonetheless, it does not translate to more clinically meaningful differences in terms of operative time and postoperative complications.

Keywords

hyperthyroidism, iodine, Lugol’s solution, thyroidectomy

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Endogenous hyperthyroidism is most commonly due to Graves’ disease or toxic nodular disease. Patients with hyperthyroidism are treated with antithyroid medications, radioactive iodine, or surgery. The advantages, disadvantages, risks, and benefits of each treatment modality should be gauged individually. Surgery is recommended for patients with the following characteristics: large goiters or low uptake of radioactive iodine, suspected or documented thyroid cancer, moderate to severe ophthalmopathy, or patient preference for surgery. Before surgery, patients should be rendered euthyroid with thionamides and β-blockers to avoid the potential of precipitating a thyroid storm during surgery.

When a patient requires urgent surgery, rapid preparation can be accomplished with a combination of corticosteroid, β-blocker, and inorganic iodide, such as iopanoic acid. Excess iodine may block the organification of iodine and decrease the synthesis of thyroid hormones, a transient phenomenon known as acute Wolff-Chaikoff effect. An escape from the Wolff-Chaikoff effect is anticipated to occur after approximately 10 days. For susceptible patients with endemic goiter and those with toxic multinodular goiter, administration of thionamides preceding that of iodide is imperative to prevent the iodine-induced hyperthyroidism (the Jod-Basedow effect).

Dr Henry Plummer was the first to propose that the administration of iodine may reduce the vascularity and friability of the thyroid gland in exophthalmic goiter, thereby making thyroidectomy easier. The finding was subsequently confirmed by several investigators. Accordingly, the guidelines of the

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American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists make a strong recommendation that “whenever possible, patients with Graves’ disease undergoing thyroidectomy should be rendered euthyroid with methimazole. Potassium iodide should be given in the immediate preoperative period” (recommendation 22). The same strong recommendation based on low-quality evidence was not modified in the updated ATA guidelines (recommendation 24), although the task force panel noticed no appreciable detriment to patient outcomes in large series when preoperative potassium iodide was not given before total thyroidectomy for Graves’ disease.7,8

In this context, a recent review gives warning of the tenuous evidence behind the ATA guidance on the preoperative use of Lugol’s iodine.9 However, several publications appear to be omitted in the literature review. Therefore, we performed this meta-analysis to clarify the benefits of preoperative iodine administration to hyperthyroid patients who are euthyroid before surgery. We hypothesized that preoperative iodine administration may be associated with decreased vascularity and reduced surgical complications.

Methods
This study was conducted in accordance with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses).10 The research question was framed in the PICO format:

- **Population:** patients with hyperthyroidism who undergo thyroid surgery
- **Intervention:** administration of any iodine-containing regimen before surgery
- **Comparison:** administration of placebo regimen or no premedication
- **Outcomes:** end points including operative time, intraoperative blood loss, blood transfusion rate, postoperative complications, perioperative mortality, and hospital stay

**Search Strategy**
We conducted a literature search in 4 databases (PubMed, Embase, Cochrane, and CINAHL) from January 1980 to June 2018. The keywords used in the search strategy included (preoperative OR pretreatment OR preparation OR thyroidectomy OR surgery), (Lugol’s OR iodide OR iodine OR iopanoic acid OR iopodate OR ipodate), and (Graves’ disease OR toxic diffuse goiter OR hyperthyroidism OR thyrotoxicosis OR Basedow’s disease OR Flajani-Basedow disease OR Flajani-Basedow-Graves disease OR Marsh’s disease OR Flajani’s disease OR Parry’s disease). Furthermore, the reference lists were hand-searched to find additional relevant works. Only English literature was considered.

**Study Selection**
All prospective and retrospective studies comparing preoperative iodine administration with no premedication before thyroidectomy were selected. The inclusion criteria were as follows: (1) studies comparing administration of any iodine-containing regimen and no administration before thyroidectomy, (2) studies reporting on the perioperative short- or long-term outcomes with a clear description of the results, and (3) studies including at least 10 patients to limit the bias potentially arising from the small sample size. Duplicated articles, review articles, editorials, case reports, letters, animal and cell studies, and other irrelevant article types were excluded. Cohort studies addressing the changes before and after iodine administration without matching of patients were also excluded.

**Data Extraction and Quality Assessment**
Two independent investigators screened titles and abstracts according to the eligibility criteria. Data abstracted from each eligible article included the following: name of first author, year of publication, country of origin, study design, number and characteristics of study participants, preoperative diagnosis, type of operation, iodine-containing regimens, and outcomes. The outcomes of interest were as follows: thyroid volume, vascularity, operative time, intraoperative blood loss, blood transfusion rate, postoperative complications, perioperative mortality, and hospital stay. Extracted data were entered into a standardized data extraction form. We applied the Newcastle-Ottawa Scale to evaluate the methodological quality of the eligible studies. Consensus on critical appraisal was reached by discussion.

**Data Synthesis and Statistical Analyses**
We used these data to calculate effect sizes for each study with Hedges’g and a standardized mean difference (SMD) for the overall pooled effect.11 The pooled risk ratios (RRs) with 95% CIs were calculated for the dichotomous data.12 A random-effects model was used throughout regardless of heterogeneity, in consideration of clinical heterogeneity. Statistical heterogeneity was assessed with the chi-square test and quantified with the I² statistic, which describes the percentage of total variation across studies that is attributed to heterogeneity instead of chance.13 Reporting bias was assessed by visual judgment of a funnel plot and by an Egger’s test.14 All statistical analyses were performed with Stata 14.0 (StataCorp, College Station, Texas).

**Results**

**Characteristics of Included Studies**
The process of the study selection for this meta-analysis is presented in Figure 1. Among full-text articles assessed for eligibility, the most common reason for exclusion was that the study was not designed to compare the preoperative administration of any iodine-containing regimen and no premedication. Two studies addressing the histologic cellular composition and antibody production were considered not clinically relevant and were excluded.15,16 Eleven studies were included in the qualitative synthesis; 2 were further excluded from the quantitative analysis. One randomized controlled study reported no difference in mean blood loss between the groups but did not have details sufficient for
The other study reported that the nadir in serum calcium after thyroidectomy was similar among groups, but it could not be incorporated into the meta-analysis. Nine studies were finally included in the meta-analysis. The 9 studies included in the meta-analysis consist of 5 randomized controlled studies and 4 observational studies. The majority of the 510 patients were diagnosed with Graves’ disease. Most were women in their thirties and forties. The type of operation was subtotal thyroidectomy in earlier studies and total thyroidectomy in more recent series, reflecting the trend of changes in surgical strategy.

Among 510 study participants, 223 (44%) had preoperative administration of various iodine-containing regimens, including Lugol’s solution, potassium iodide, and the saturated solution of potassium iodide. The remaining 287 (56%) either did not have iodine administration or had placebo administration (1 study). The intervention details are presented in Table 2.

**Narrative Synthesis**

Before 2000, 3 randomized studies from the United Kingdom addressing the effects on vascularity and intraoperative blood loss showed conflicting results. The only study that detected a difference pointed out that the decrease in thyroid blood flow was minimal among patients with low initial flow. A small retrospective series from the United States suggested that iodine administration did not reduce intraoperative blood loss.

Between 2000 and 2010, 2 retrospective studies from Germany and Japan reported that iodine administration did not change thyroid vascularity or intraoperative blood loss. Interestingly, Hassan et al observed an increase in early postoperative complications among patients receiving preoperative Lugol’s solution, probably reflecting a selection bias.

From 2010 to 2018, two randomized studies from Turkey and the United States supported that iodine administration reduced blood loss during thyroidectomy. A prospective cohort study from the United States revealed that preoperative potassium iodide was associated with less transient hypoparathyroidism and transient hoarseness but did not change the overall difficulty of thyroidectomy.

**Effects of Iodine on Perioperative Findings**

Six studies assessed thyroid volume (n = 3) or weight (n = 3). The pooled mean thyroid volume was 92 mL and 70 mL in the iodine administration group and the control group, respectively. The pooled mean thyroid weight was 36 g and 39 g in the iodine administration group and the control group, respectively. As shown in Figure 2a, preoperative iodine administration did not significantly influence thyroid volume/weight (SMD, 0.00; 95% CI, –0.26 to 0.26), with little heterogeneity among studies ($I^2 = 5\%$).

Five studies assessed thyroid vascularity by blood flow (n = 3) or blood vessel density (n = 3). Blood flow was measured with color Doppler ultrasonography and calculated from the vessel’s diameter and the time-averaged blood velocity of the superior thyroid artery or from peak systolic and diastolic velocities of the 4 main thyroid arteries. Blood vessel density was obtained by counting the number of blood vessels within a given area without specific staining or with immunohistochemical staining of the endothelial marker CD31 or CD34. Overall, preoperative iodine administration could decrease thyroid vascularity (SMD, 0.87; 95% CI, 0.23 to 1.51), with significant heterogeneity among studies ($I^2 = 75\%$; Figure 2b).

Two studies assessed the operative time. Total or near-total thyroidectomy was performed in 1 study, and the type of operation was not specified in the other. The pooled mean operative time was 116 minutes and 130 minutes in the iodine administration group and the control group, respectively. As shown in Figure 2c, preoperative iodine administration did not significantly influence the operative time (SMD, 0.11; 95% CI, –0.36 to 0.59), with moderate heterogeneity ($I^2 = 30\%$).

Five studies assessed intraoperative blood loss by volume (n = 3) or by weight (n = 2). The pooled mean blood loss was 65 mL and 147 mL, or 91 g and 114 g, in the iodine administration group and the control group, respectively. As shown in Figure 2d, preoperative iodine administration could decrease intraoperative blood loss (SMD, 0.80; 95% CI, 0.23 to 1.37), with significant heterogeneity among studies ($I^2 = 72\%$; Figure 2d).
Effects of Iodine on Postoperative Complications

Five studies assessed the occurrence of temporary (n = 2) or permanent (n = 5) vocal cord palsy. The pooled risk of temporary vocal cord palsy was 10% and 8% in the iodine administration group and the control group, respectively. The pooled risk of permanent vocal cord palsy was 0% and 1% in the iodine administration group and the control group, respectively. Overall, preoperative iodine administration was associated with a lower risk of vocal cord palsy.

Table 1. Patient Characteristics of the Included Studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Participants</th>
<th>Diagnosis</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randle19 (2018)</td>
<td>US</td>
<td>Prospective</td>
<td>Female: 44 of 59 (75%); age, 42.7 ± 13.5 y</td>
<td>Graves' disease</td>
<td>Total thyroidectomy</td>
</tr>
<tr>
<td>Whalen20 (2017)</td>
<td>US</td>
<td>RCT</td>
<td>Female: 27 of 33 (82%); age, 40.2 ± 11.5 y</td>
<td>Graves' disease</td>
<td>Total or near-total thyroidectomy</td>
</tr>
<tr>
<td>Yilmaz21 (2016)</td>
<td>Turkey</td>
<td>RCT</td>
<td>Female: 32 of 40 (80%); age, 43.0 ± 8.4 y (range, 25-63)</td>
<td>Hyperthyroidism (Graves' disease or multinodular goiter)</td>
<td>Total thyroidectomy</td>
</tr>
<tr>
<td>Yabuta22 (2009)</td>
<td>Japan</td>
<td>Retrospective</td>
<td>Female: 86 of 113 (76%); age, 32.7 ± 12.2 y</td>
<td>Graves' disease</td>
<td>Surgical treatment</td>
</tr>
<tr>
<td>Hassan23 (2008)</td>
<td>Germany</td>
<td>Retrospective</td>
<td>Female: 123 of 153 (80%); median age, 33 y (male) and 36 y (female); (range, 10-75)</td>
<td>Graves' disease</td>
<td>Subtotal, near-total, or total thyroidectomy</td>
</tr>
<tr>
<td>Erbil24 (2007)</td>
<td>Turkey</td>
<td>RCT</td>
<td>Female: 30 of 36 (83%); age, 41.9 ± 11.0 y (range, 14-61)</td>
<td>Graves' disease</td>
<td>Total or near-total thyroidectomy</td>
</tr>
<tr>
<td>Marmon25 (1989)</td>
<td>US</td>
<td>Retrospective</td>
<td>Female: 32 of 42 (76%); age, 30.2 y (range, 16-62)</td>
<td>Hyperthyroidism</td>
<td>Subtotal thyroidectomy</td>
</tr>
<tr>
<td>Kaur26 (1988)</td>
<td>UK</td>
<td>RCT</td>
<td>Female: 16 of 22 (73%); age, 33.7 ± 9.3 y</td>
<td>Graves' disease</td>
<td>Partial thyroidectomy</td>
</tr>
<tr>
<td>Chang27 (1987)</td>
<td>UK</td>
<td>RCT</td>
<td>Female: 10 of 12 (83%); age, 31.7 ± 8.8 y (range, 19-50)</td>
<td>Graves' disease</td>
<td>Bilateral subtotal thyroidectomy</td>
</tr>
</tbody>
</table>

Abbreviation: RCT, randomized controlled trial.

Table 2. Interventions and Outcomes of the Included Studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randle19 (2018)</td>
<td>Treatment (n = 25): potassium iodide, 1 qtt tid × 10 d</td>
<td>Thyroid weight, complications</td>
</tr>
<tr>
<td></td>
<td>Control (n = 34): none</td>
<td></td>
</tr>
<tr>
<td>Whalen20 (2017)</td>
<td>Treatment (n = 18): SSKI, 8 qtt/d × 7 d</td>
<td>Operative time, blood loss, complications</td>
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<tr>
<td></td>
<td>Control (n = 15): none</td>
<td></td>
</tr>
<tr>
<td>Yilmaz21 (2016)</td>
<td>Treatment (n = 20): Lugol’s solution, 0.8 mg/kg × 10 d</td>
<td>Thyroid volume, blood flow, blood loss, complications</td>
</tr>
<tr>
<td></td>
<td>Control (n = 20): none</td>
<td></td>
</tr>
<tr>
<td>Yabuta22 (2009)</td>
<td>Treatment (n = 89): potassium iodide, 64.6 ± 18.3 mg/d × 11.0 ± 3.7 d</td>
<td>Thyroid volume, operative time, blood loss</td>
</tr>
<tr>
<td></td>
<td>Control (n = 24): none</td>
<td></td>
</tr>
<tr>
<td>Hassan23 (2008)</td>
<td>Treatment (n = 16): β-blocker + Lugol’s solution, 3-6 qtt/d × 3-12 d</td>
<td>Micravessel density, complications</td>
</tr>
<tr>
<td></td>
<td>Control (n = 137): none</td>
<td></td>
</tr>
<tr>
<td>Erbil24 (2007)</td>
<td>Treatment (n = 17): Lugol’s solution, 10 qtt/d × 10 d</td>
<td>Thyroid volume, blood flow, microvessel density, blood loss</td>
</tr>
<tr>
<td></td>
<td>Control (n = 19): none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control (n = 20): none</td>
<td></td>
</tr>
<tr>
<td>Kaur26 (1988)</td>
<td>Treatment (n = 10): Lugol’s solution, 0.4 mL tid × 10 d</td>
<td>Thyroid size, blood vessel density, blood loss, hospital stay, complications</td>
</tr>
<tr>
<td></td>
<td>Control (n = 12): none</td>
<td></td>
</tr>
<tr>
<td>Chang27 (1987)</td>
<td>Treatment (n = 6): Lugol’s solution, 0.3 mL tid × 9 d</td>
<td>Thyroid weight, blood volume flow</td>
</tr>
<tr>
<td></td>
<td>Control (n = 6): placebo</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: qtt, drops; SSKI, saturated solution of potassium iodide; tid, 3 times per day.
administration did not significantly influence the risk of vocal cord palsy (log-transformed RR, –0.11; 95% CI, –2.56 to 2.34), with significant heterogeneity among studies ($I^2 = 72\%$; Figure 3a). Five studies assessed the development of temporary ($n = 3$) or permanent ($n = 4$) hypoparathyroidism/hypocalcemia. The pooled risk of temporary hypoparathyroidism or hypocalcemia was 17% and 19% in the iodine administration group and the control group, respectively. The pooled risk of permanent hypoparathyroidism/hypocalcemia was 3% and 5% in the iodine administration group and the control group, respectively. Overall, preoperative iodine administration did not significantly influence the risk of hypoparathyroidism/hypocalcemia (log-transformed RR, –0.19; 95% CI, –1.49 to 1.12), with moderate heterogeneity among studies ($I^2 = 65\%$; Figure 3b).

Five studies assessed the occurrence of hemorrhage or hematoma after thyroidectomy. The pooled risk of hemorrhage/hematoma was 4% and 1% in the iodine administration group and the control group, respectively. As shown in Figure 3c, preoperative iodine administration did not significantly influence the risk of postoperative hemorrhage/hematoma (log-transformed RR, –1.14; 95% CI, –3.90 to 1.63), with moderate heterogeneity among studies ($I^2 = 66\%$).

Only 1 study, published in 1988, assessed the length of hospital stay. The mean length of postoperative hospital stay was 6.7 days and 9.0 days in the Lugol’s solution group and the control group, respectively, without a statistically significant difference (SMD, 0.86; 95% CI, –0.03 to 1.74).

**Adverse Events Associated with Iodine Administration**

No adverse events associated with iodine administration were reported in the included studies. The histologic morphology—particularly lymphocyte infiltration and fibrosis—was similar between the groups. Moreover, iodine administration did not influence antimicrosomal antibody titers.

**Reporting Bias**

Funnel plots were drawn for each outcome containing ≥3 studies and assessed for symmetry. As shown in Figure 4, we found limited publication bias or none regarding thyroid volume, thyroid vascularity, and intraoperative blood loss.

**Sensitivity Analysis**

Sensitivity analyses were performed to assess the impact of observational studies. To this end, we conducted second analyses composed of the 5 randomized controlled studies only. There was no significant difference in thyroid volume with or without preoperative iodine administration (SMD, 0.07; 95% CI, –0.30 to 0.45; $I^2 = 0\%$). Furthermore, the difference in thyroid vascularity (SMD, 1.06; 95% CI, 0.42 to
1.71; $I^2 = 67\%$) and intraoperative blood loss (SMD, 1.07; 95% CI, 0.70 to 1.44; $I^2 = 0\%$) remained statistically significant. The heterogeneity decreased when only randomized controlled studies were examined. While the number of randomized controlled studies was too small to perform a pooled analysis of the risk of vocal cord palsy or hypoparathyroidism/hypocalcemia, there was no difference in the risk of postoperative hemorrhage/hematoma (log-transformed RR, 0.18; 95% CI, –2.02 to 2.38; $I^2 = 0\%$).

Collectively, the sensitivity analyses gave similar results, consistent with the main analysis.

**Discussion**

Hypervascularity in association with hyperthyroidism, particularly Graves’ disease, may increase operative difficulty and heighten the risk of postoperative complications. Thyroid blood flow is directly proportional to the vascular density of the thyroid gland, the glandular weight, the severity of Graves’ disease, and intraoperative blood loss.28 A diagnosis of hyperthyroidism is independently associated with a difficult thyroidectomy.29 In a recent systematic review, among various indications for thyroidectomy, Graves’ disease is the only one with an increased risk of postoperative hematoma.30 Excessive bleeding during thyroidectomy can hamper the delineation of anatomy and the preservation of critical structures, such as the recurrent laryngeal nerve and parathyroid glands. In this regard, several attempts have been made to decrease blood flow to the thyroid in the hope, ultimately, of decreasing operative complications.

Since Plummer’s original observation5 of the beneficial effect of Lugol’s solution on the prevalence of postoperative thyroid crisis, the use of Lugol’s solution has been widely adopted. Once thionamides and $\beta$-blockers became clinically available, the prime use of iodine-containing regimens for thyrotoxicosis control is no longer preferred. Nonetheless, many surgeons continue preoperative iodine administration based on the belief that thyroid vascularity and friability will be further reduced. Several iodine-containing regimens are available, and the doses used in studies vary considerably.31 This meta-analysis confirmed keen observations for decades that when compared with no iodine administration, preoperative iodine-containing regimens effectively decrease the vascularity of the thyroid gland in terms of blood flow or blood vessel density. In cultured human thyroid follicles and FRTL-5 thyroid cells, excess iodide downregulates the expression and secretion of vascular endothelial growth factors.32,33 Furthermore, iodine load may modulate the expression levels of the immunity-associated genes. When thyroid follicles were cultured in high-iodide medium, the expression of several chemokines (CCL2, CXCL8, and CXCL14) was upregulated.34 Recently, Huang and colleagues demonstrated that Lugol’s solution significantly decreased serum levels of vascular endothelial growth factor and IL-16 among patients with Graves’ disease.35

**Figure 3.** Forest plots comparing postoperative complications between the preoperative iodine group and the control group: (a) vocal cord palsy, (b) hypoparathyroidism, and (c) hemorrhage or hematoma. The log-transformed risk ratio (RR) is shown with 95% CIs.
In our meta-analysis, the decrease in thyroid vascularity was accompanied by a marked reduction in intraoperative blood loss. Nonetheless, this benefit does not necessarily translate to a difference in clinical outcomes in terms of postoperative complications. This is consistent with the findings of a recent report showing that postoperative complications in Graves’ disease were not correlated with the amount of intraoperative blood loss.\textsuperscript{36} In accordance, experienced surgeons have argued that thyroidectomy without preoperative iodine administration can be safely performed for patients with well-controlled hyperthyroidism.\textsuperscript{8,37-39} Given our findings of no differences in complication rates, preoperative iodine administration may be considered optional rather than mandatory.

Excess iodine not only inhibits the thyroid peroxidase, thus attenuating the oxidation and organification of thyroid hormones, but also blocks the release of thyroid hormones.\textsuperscript{40} As such, iodine administration increases intrathyroidal colloid and raises intrathyroidal pressure.\textsuperscript{41} Indeed, an increased colloid formation leading to the compression of intrathyroidal vasculature and lymphatics was speculated as the mechanism for decreased perfusion, which makes the thyroid gland less vascular. Physicians have noted that some patients experience pressure sensations in the neck following iodine administration, as a result of the “firming up” of the goiter.\textsuperscript{42} Theoretically, it makes the thyroid gland firmer in consistency, less friable, and thus easier to handle. Nonetheless, surgeons from Kuma Hospital noticed that thyroid volume in Graves’ disease can increase with iodide administration independent of thyroid-stimulating hormone stimulation.\textsuperscript{22} The present meta-analysis showed no difference in thyroid volume or weight with or without iodide administration. In our experience, iodide administration would sometimes, paradoxically, make surgery even more difficult in certain cases because of thyroid enlargement or firmness.

Operative time was reported in 2 studies, and our meta-analysis revealed that preoperative iodine administration does not influence operative time. It is uncertain whether the analysis was underpowered or the 2 strategies were not sufficiently different from each other. Vascularity is not the only factor determining operative time. A thyroidectomy

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{funnel_plots}
\caption{Funnel plots for publication bias in studies comparing the standardized mean difference (SMD) between the preoperative iodine group and the control group: (a) thyroid volume, (b) thyroid vascularity, and (c) blood loss.}
\end{figure}
difficulty scale composed of 4 items (vascularity, friability, mobility/fibrosis, and gland size) was developed to correlate subjective difficulty with operative time and complications. In a recent study, investigators found that preoperative potassium iodide slightly increased the mobility/fibrosis score of the thyroid gland, albeit without a statistically significant difference. It is noteworthy that the study participants included in the meta-analysis typically had a small to medium thyroid size (pooled thyroid weight <40 g, pooled volume <100 mL). We assume that an enriched colloid formation following iodine administration, in turn increasing the thyroid firmness and decreasing the mobility, may enhance surgical difficulty in large goiters.

Whereas there is no doubt that preoperative iodine administration does decrease vascularity, it is difficult to draw meaningful conclusions regarding the effects on the safety of thyroidectomy. Although the adverse effects of high iodine-containing regimens seem uncommon, they are usually corrosive and taste unpleasant. To decrease thyroid vascularity, an alternative approach is to extend the duration of antithyroid medications and serially monitor the vascularity of the thyroid gland by ultrasound. We are in agreement with the findings of a previous report that clearly demonstrated that longer duration of drug treatment is helpful in reducing vascularity and intraoperative bleeding. Certainly, it is important not to induce an oversuppression of thyroid function and render patients hypothyroid, because the accompanying thyroid-stimulating hormone activation may, on the contrary, lead to increased vascularity and thyroid glandular size.

The present study is the first analysis that summarizes and combines the published evidence focusing on the impact of preoperative iodine administration on surgical outcomes. The strength of this study is that a number of randomized studies were included, with a low level of reporting bias. However, the present study has some limitations that warrant consideration when interpreting the results. First, the dosing and regimes of preoperative iodine vary across studies, and antithyroid medications were not standardized. The severity and duration of hyperthyroidism were not specified or controlled in most studies, even though patients were euthyroid at the time of surgery. These factors are the main sources of clinical heterogeneity and may mix the intervention effects. Second, each hospital might have performed operations and evaluated complications according to different local policies, which may induce performance bias and detection bias. Third, our included literature spanned 30 years, which might have led to inconsistencies in the surgical approach (subtotal vs total thyroidectomy) and technique (eg, the use of energy-based devices). These inconsistencies may have influenced the results. Finally, studies published in non-English languages were excluded. Further well-designed, properly powered randomized controlled studies are warranted to investigate the possible benefits of preoperative iodine administration and guide clinical practice in the modern era.

For hyperthyroid patients who are euthyroid in the preoperative phase and have small to medium thyroid size, iodine administration may decrease thyroid vascularity and intraoperative blood loss. Nonetheless, it does not result in any additional benefits at surgery, including shorter operative time or lower complication rates. Our findings do not support the guideline recommendation that preoperative iodine be given before surgery for most patients with Graves’ disease who are already taking antithyroid medications to control thyrotoxicosis. We propose that its use may be considered for patients who are unable to take thionamides or have a short duration of treatment with thionamides and those who require rapid preparation for surgery.

Author Contributions
Chung-Hsin Tsai, conception and design; acquisition, analysis, and interpretation of data; drafting and revision of the manuscript; final approval; Po-Sheng Yang, acquisition, analysis, and interpretation of data; revision of the manuscript; final approval; Jie-Jen Lee, conception and design; analysis and interpretation of data; revision of the manuscript; final approval; Tsang-Pai Liu, conception and design; revision of the manuscript; final approval; Chi-Yu Kuo, conception and design; revision of the manuscript; final approval; Shih-Ping Cheng, conception and design; acquisition, analysis, and interpretation of data; drafting and revision of the manuscript; final approval.

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