Archives of Surgical Research | Meta-Analysis

Preoperative Use of Lugol's Iodine in Graves' Disease- Clearer Surgical Field but No Effect on Outcomes: A Meta-analysis of Controlled Studies

Safia Zahir Ahmad, Zaitoon Zafar, Nida Maryam, Talat Waseem

BACKGROUND Recently, the American Thyroid Association (ATA) assessed their guidelines regarding the treatment of Graves' disease and its compliance. These guidelines emphasized on preoperative treatment with Lugol's Iodine before surgery, but said guidelines are based on historical practice rather than on evidence to the benefit of Lugol's Iodine in the preoperative period. We conducted a meta-analysis to analyse the effect of Lugol's Iodine in the preoperative patient with Graves' disease.

DATA SOURCE Studies were identified using the Medical Subject heading and free-text words: "Graves'' disease" "Thyroidectomy" "Preoperative Treatment" "Lugol's Iodine" "Potassium Iodine" "Hyperthyroidism" in Pubmed Central, Pubmed, Cochrane, Embase, ICTRP, CINAHL and Google Scholar.

METHODS Randomized and controlled studies which compared the Lugol's Iodine therapy with non Lugol's Iodine or placebo therapy prior to thyroidectomy for Graves'' disease were included in the study. Single arm study, non-comparative study, euthyroid and non-toxic thyroid nodules were excluded from the study. Meta-analysis data was assessed using random effect with pooled results using mean difference and Odd's ratio where applicable. Outcomes assessed were intraoperative and postoperative parameters.

RESULTS We found 4 randomised control trial and 6 comparative studies which compared the effect Lugol's Iodine with non-Lugol's Iodine in the preoperative period in a patient of Graves' disease. A total of 977 patients were identified with 372 administered Lugol's Iodine and 605 not administered Lugol's Iodine in the preoperative phase. Mean blood flow, vascular density and estimated blood loss was significant in patients who were administered preoperative Lugol's Iodine solution, while there was no significant difference in difficult thyroidectomy scale, thyroid volume, and post-operative outcomes such as mean-operative time, hypocalcaemia, vocal cord paresis, hematoma formation in both the groups.

CONCLUSION Administration of Lugol's Iodine decreases the vascularity and estimate blood loss intraoperatively, but has no effect on difficult thyroidectomy scale, its volume and weight and on postoperative parameters. We found no clinical evidence that Lugol's Iodine improves patient outcomes.

KEY WORDS Graves' Disease, Thyroidectomy, Lugol's Iodine, Preoperative preparation, Hyperthyroidism

HOW TO CITE: Ahmed SZ, Zafar Z, Waseem T, Maryam N, Azim KM. Preoperative Use of Lugol's Iodine in Graves' Disease- Clearer Surgical Field but No Effect on Outcomes: A Meta-analysis of Controlled Studies *Archives of Surgical Research*. 2020;1(1):3-13.
https://doi.org/10.48111/2020.01.02

Meta-Analysis

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Thyrotoxicosis is one of the more common endocrine conditions, having an incidence of 1 in 2000 in the European population[1], 1.2% in the U.S. population and 1 to 1.5 % in the general global population. Within the thyrotoxicosis spectrum, Graves' disease is the most common presentation[2]. Graves' disease is an autoimmune disorder and various treatment option exist to treat the condition[3]. The initial treatment options are: medical management with antithyroid drugs which are well tolerated with a success rate of approximately 50%, when given for 12-18 months or Radioactive Iodine (I-131) can be administered in cases where indicated[4]. However, the definite cure for this condition is surgical treatment when other options fail, or relapses occur. To surgically excise the thyrotoxic thyroid in the form of subtotal or total thyroidectomy is the preferred surgical treatment of choice. The patient is optimized preoperatively with antithyroid drugs and Lugol's Iodine is given before the procedure[5]. It is an ongoing historical practice which was introduced in 1920 and has been established as standard practice [6]. Preoperatively, 10 drops are given, three times a day for 7-10 days. The practice of dosage and the duration of Lugol's Iodine given preoperatively varies globally. Since the introduction of this practice, advances in medical practice have introduced

various other medications, such as beta-blockers, thiouracil derivatives etc.[7].

The ATA and other clinical endocrinologists have introduced guidelines to manage thyrotoxicosis prior to surgical thyroidectomy. The requirement for preparing for thyroidectomy is in order to reduce bring the patients to a euthyroid state with methimazole medication. In urgent cases, where immediate thyroidectomy is required or in patients who are allergic to antithyroid medication, beta-blockers and Lugol's Iodine is used[8]. However, these guidelines are adherent to a historically preferential practice and the efficacy of the preparatory treatment has not been validated.

Based on the ATA guidelines, which recommend strongly the use of Lugol's Iodine, Tsai and his colleagues performed the first meta-analysis study reviewing the surgical outcomes of preoperative treatment with Lugol's Iodine[9]. The study demonstrated that there was a decrease in vascularity and blood flow but there was no difference in the complication rates. The study was limited due to a small sample size available in the literature. Recently, a large sample size has become available in medical literature, which can aid in reaching a more precise conclusion.

The aim of this meta-analysis is to compare the outcomes of Lugol's Iodine on preoperative preparation for Graves' disease before surgery with controlled studies which did not administer Lugol's Iodine. By adding the recent large sample size-controlled study to the previous conducted meta-analysis to review the effect of the Lugol's Iodine in vascularity and complication rates.

MATERIAL AND METHODS:

Search Strategy and inclusion:

A comprehensive literature search of randomized controlled and non-randomized controlled trials conducted on the database of Pubmed, Cochrane library, Pubmed Central, Embase, ICTRP, CINAHL and Google Scholar and studies were time framed from 1985 to 2020. The Medical Subject Heading, and the free text used in the search "Graves'' Disease" "Thyroidectomy" "Preoperative treatment" "Potassium Iodide" "Lugol's Iodine" and "Hyperthyroidism". Further studies were extracted, and data was explored using the cited authors and references. Boolean Operator method was used for studies exploration. All language barriers were overcome.
All comparative controlled trials which used the intervention of any form of Iodine therapy for preoperative preparation prior to a total/subtotal thyroidectomy in order to optimise the thyrotoxicosis to a euthyroid state were included in the study. Studies mentioning the vascularity, difficulty index of thyroidectomy, thyroid volume, and weight, per operative outcomes and complication rates were included.
Single arm studies/ non-comparative studies, duplicate studies, reviewer letters, abstracts with no full articles were excluded. Trials with multi-arm studies and management, studies with radioactive Iodine therapy and studies without clear description of outcomes, qualitative study, study size of less than 10, were excluded to avoid confounding bias.

Study Selection and Outcome:

All prospective and retrospective controlled studies that compared preoperative Lugol's Iodine therapy with placebo or non-Iodine therapy prior to total/subtotal thyroidectomy in Graves' disease were included in this study. The primary outcomes analyzed were difficulty thyroidectomy scale, thyroid volume, thyroid weight, mean blood flow, vascular density, resistance index, estimate blood loss, and post-operative outcomes in terms of mean-operative time, hypocalcaemia, vocal cord paresis and hematoma. The outcomes measured were quantitative variables.

Data Extraction:

The selected studies were identified and Preferred Reporting of Items of Systematic Review and Meta-analysis (PRISMA) guidelines were observed[10]. Two Authors reviewed the articles and screened the selected studies from the extensive literature search. Data was explored further by the third author to identify discrepancy and was discussed. Duplicate studies and the studies that were excluded were reviewed by the third author to confirm the decision. Eligibility criteria was discussed further in case of queries. Included studies were counterchecked and in case of doubt, were explored further. The quality of the randomized controlled trial studies was observed using Cochrane Collaboration risk of bias tool[11]. Random sequence and allocation concealment were used to assess the selection bias, blinding the patient and personnel was used to for performance bias, reporting bias, detection bias and attrition bias was reviewed. The study scoring more than 4 was considered as a high-quality study. For non-randomized comparative trial, ROBIN-1 of intervention assessment tool was used[12]. The preintervention domain used to detect selection bias, at intervention domain was used to assess bias in classification of intervention and postintervention domain was used to assess to detect performance, detection, attrition, and reporting bias. Consensus was reached after discussion and critically appraised.

Data Analysis:

After reviewing and discussing the quality of the studies, meta-analysis was performed on the selected studies with comparable studies and the outcomes were assessed using continuous and dichotomous variables, where appropriate, of patients who received preoperative Lugol's Iodine

compared to who did not, prior to a thyroidectomy. The continuous variables were calculated using mean difference with inverse variance and dichotomous variable using Odd's ratio with Mantel-Haenzel method with 95% confidence interval. Studies in which median range were calculated, mean and standard deviation was extracted after conversion. Random and fixed effect method was used as accordingly to the heterogeneity of the population with a cut-off of 50%. The meta-analysis data was quantified and calculated using 2x2 chi-squared test in RevMan 5.4 software.

The sensitivity of the studies was analyzed by excluding individual studies and reviewed the pooled results to review if the pooled results are influenced by it. Q test and I^2 test was used for statistical analysis for heterogeneity assessment within the studies. The pooled results of the intervention were described in Forest Plot and the publication bias was assessed using Funnel plot.

RESULTS:

After extensive literature search using Boolean method, 2150 articles were found, 60 full text articles were reviewed for eligibility, irrelevant studies were excluded. 10 articles were identified and selected, which fulfilled the inclusion criteria, after a detailed review. The articles excluded were due to nature of non-comparative/single arm study, non-availability of full text form, unclear results, studies which included I-131 therapy, multiple arm management studies, limited abstracts and qualitative studies. The PRISMA flow chart shown in Fig 1.

The selected 10 studies include 4 randomized control trial[13-16]and 6 non-randomized control trial[17-22]. The characteristics of the studies is shown in Fig 2. Out of 10, two studies were retrospective while rest were prospective. All the studies were conducted on Graves' disease, toxic goitre, and hyperthyroidism. Lugol's solution was given in 6 studies while 4 studies administered potassium iodide in the intervention group with none given in control groups. Duration of the intervention given in six studies was 10 days of preoperative Lugol's Iodine prior to the surgery while 2 study gave 7 days and 13 days, respectively. Most of the patient of Graves' disease underwent near or total thyroidectomy except in the Kaur et al. study, which included partial thyroidectomy and Yabuta et al. did not mention the type of surgical treatment performed.

A total of 977 patients where included in the study with 372 patient's receiving Lugol's Iodine in the preoperative period and 479 patients not receiving the intervention. In RCT group, 67 participants received Lugol's Iodine while 64 did not. In Non-RCT group, 305 were identified who had received the preoperative preparation of Lugol's Iodine while 541 did not receive the intervention.

The quality of the 4 randomized control trial showed low risk on Cochrane Collaboration assessment tool as shown in Fig 3. The Non-randomized control trial was assessed using the Cochrane risk of bias in nonrandomized studies of interventions showing moderate risk of bias in few domains as in Fig 4.

Difficult thyroidectomy scale parameter was mentioned in two studies with 43 patient who received Lugol's Iodine in preoperative phase while 49 did not receive the treatment. The pooled results showed no significant difference in both the groups with P value of 0. Moreover, 3 articles assessed the thyroid weight, in Lugol Iodine group, 166 patients were reviewed and 488 in non Lugol's Iodine Group. The mean thyroid weight in non-Lugol's Iodine was found 44g as compared to who received Lugol's Iodine was 61g with mean difference in pooled result of 15.3% with heterogeneity of 93%.

Regarding thyroid volume, 3 studies reviewed, and pooled results of mean thyroid volume found was 74mls in LI group and 68mls in non-Lugol's Iodine group with no significant difference in P value with pooled result of mean difference 2.9% (95% CI -5 to 11%) with a low heterogeneity among the study.

Thyroid vascularity was observed in 5 studies by assessing the mean blood flow and vascular density. The thyroid vascularity was assessed by colour flow Doppler ultrasonography identifying the four vascular pedicles and monitoring the peak systolic and diastolic velocity, vessel diameter and blood flow. The resistance index was noted and sampled at the entrance of the thyroid gland. The microvascular density was assessed by the vessels with number of areas covered with staining or without staining. The overall pooled results show significant difference in the group who received Lugol's solution preoperatively causing reduction in the thyroid vascularity.

Moreover, 5 studies reviewed the estimate blood loss in thyroidectomy with 156 in Lugol Iodine group and 88 in Non-Lugol's Iodine group. The pooled results of mean difference were 62.40% (95% CI 102-22%) with random effect model and heterogeneity of 84%, and favoured patient who received Lugol's Iodine due to the reduction in the thyroid vascularity during the procedure.

Mean operative time was reviewed in 4 studies with total of 647 patients, 257 in Lugol Iodine group and 390 in the non-Lugol's Iodine group. The mean difference in pooled results were 100 min in Lugol's Iodine group and 101 min in non Lugol's Iodine group with 0.15% (95% 1.7 -2%) showing no effect in the results of both the groups.

Postoperative parameters in terms of hypocalcaemia and vocal cord paralysis were observed in five studies and hematoma in four. The pooled results were calculated with Odd's ratio, random effect model and moderate

heterogeneity was found. Outcomes showed no difference in both the groups.

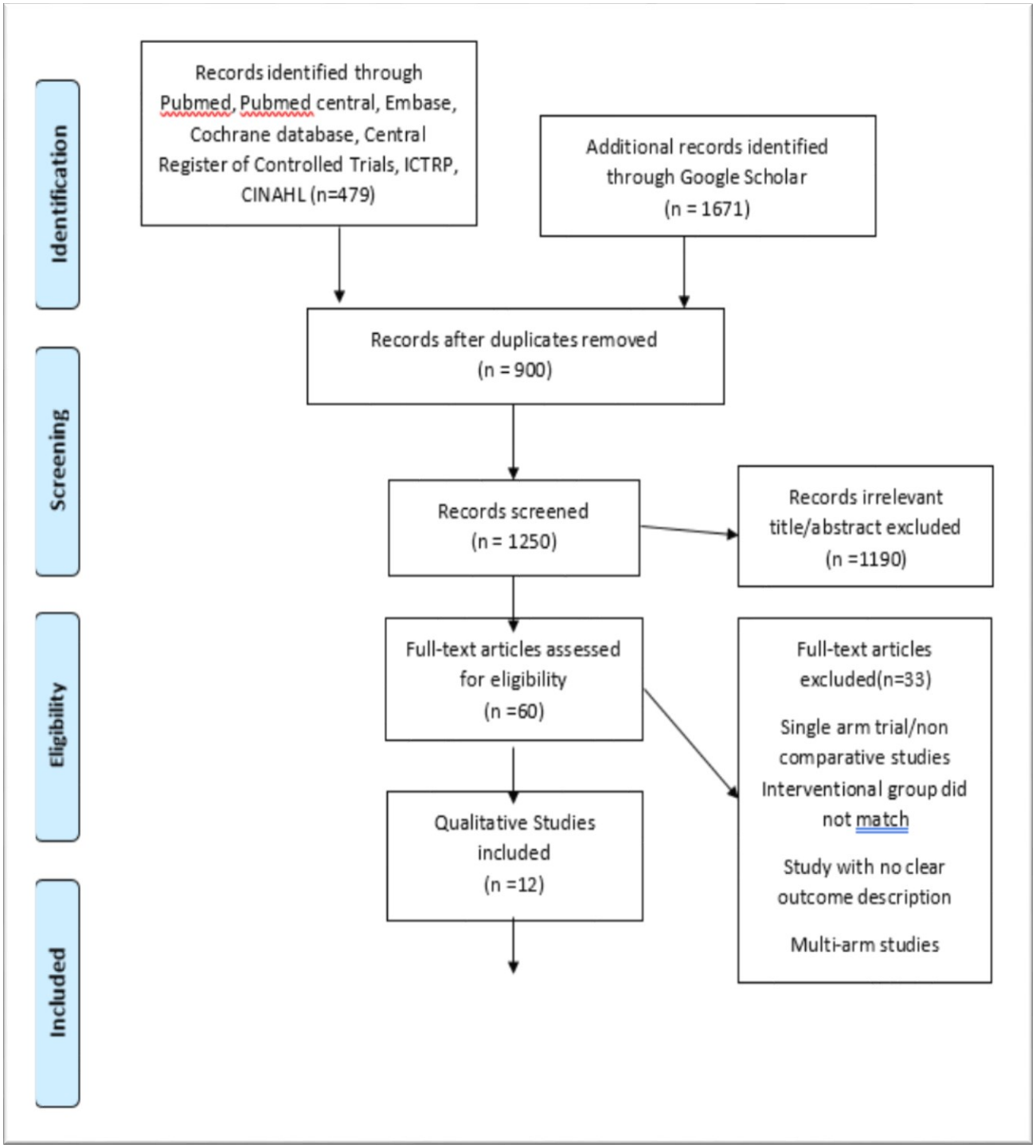


Fig 1: Flow Chart of studies included using PRISMA guidelines.

Characteristics of Studies, its Intervention and Outcomes

Authors	Study Design	No. of Patient in LI	No. of Patients in Non LI	Age	Diagnosis	Procedure	Intervention	Outcomes
Whalen 2017	RCT	18	15	40.2±11.5	Graves' Disease	Total Thyroidectomy	SSKI, 8 qtt/d in 7 days, control: none	Operative time, blood loss, complication
Yilmaz 2016	RCT	20	20	43.0±8.4	Graves' Disease/Toxic Multinodular goiter	Total Thyroidectomy	Lugol's solution, 0.8 mg/kg in 10 d, Control :None	Thyroid volume, blood flow,blood loss, complication
Erbil 2007	RCT	17	19	41.9±11.07	Graves' Disease	Near/Total Thyroidectomy	Lugol's solution, 10 qtt/d in 10 d, Control: None	Thyroid volume, blood flow, microvessel density, blood loss
Kaur 1988	RCT	12	10	33.7+9.34	Graves' Disease	Partial Thyroidectomy	Lugol's solution, 0.4 mL tid in 10 d, Control:None	Thyroid size, blood vessel density, Estimate blood loss, hospital stay, complication
Randle 2018	Non-RCT (Prospective)	25	34	42.7±13.5	Graves' Disease	Total Thyroidectomy	potassium iodide, 1 qtt tid in 10 d, control: None	Thyroid weight , complication
Yabuta 2009	Non-RCT (Retrospective)	89	24	32.7±12.2	Graves' Disease	Surgery	potassium iodide, 64.6± 18.3 mg/d in 11.0± 3.7 d, control :None	Thyroid volume, operative time, blood loss
Hassan 2008	Non-RCT (Retrospective)	16	137	Median:33 (male),36 (Female)(Range 10-75)	Graves' Disease	Near/Subtotal/Total Thyroidectomy	B-blocker, Lugol's solution, 3-6 qtt/d in 3-12 d, control: None	Microvessel density, complications
Linder 2020	Non-RCT (Prospective)	125	317	Median:37in KI (12-77), 45 in Non-KI(11-80)	Graves' Disease/Hyperthyroidism	Total Thyroidectomy	Vitamin C+ Potassium Iodide, 3qtt bid in 13 days, Control: None	Thryroid weight, operative time, hospital stay, Complications
Ansaldo 2000	Non-RCT (Prospective)	25	19	Median:32(24-56)	Diffuse Toxic Goiter	Near Total Thyroidectomy	Lugol Solution starting with 5qtt to 15 qtt in 7 days, Control: None	Resistance index of thyroidal artery flow, blood loss
Huang 2015	Non-RCT (Prospective)	25	10	32.2±5.6	Graves' Disease	Near Total Thyroidectomy	Treatment: Lugol Solution 10qtt in 10 days, Control :None	Blood Flow, VEGF, IL-16

Fig 2: Characteristics of the included study. LI: Lugol's Iodine, KI: Potassium Iodide, RCT: Randomized control trial, VEGF: Systemic angiogenic factor, IL-16: Interleukin 16

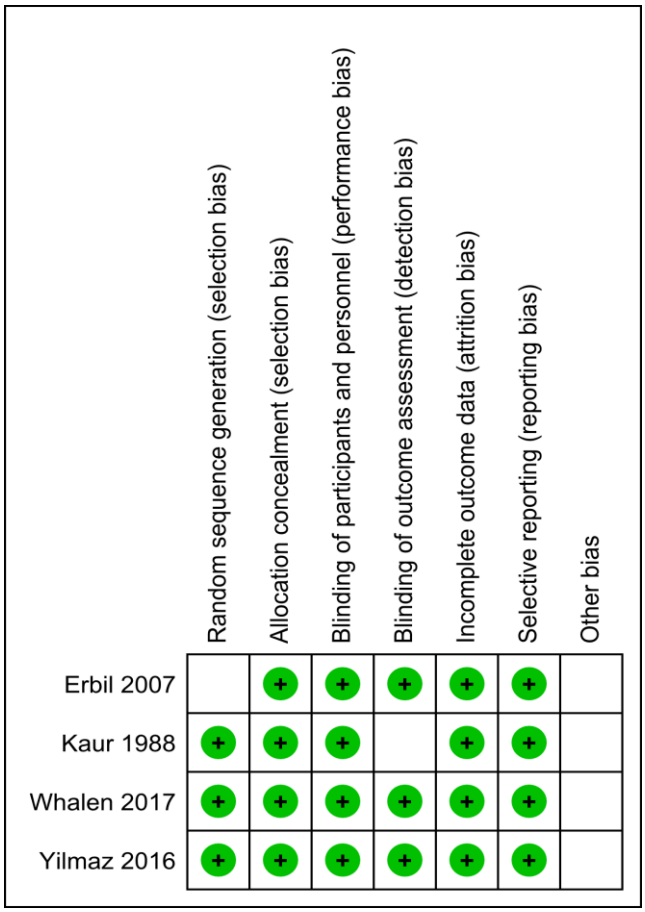


Fig 3: Cochrane Risk of Bias Assessment tool for Randomized Control Trial.

The sensitive analysis of the randomized articles was reviewed individually, exploring the effect on the pooled results. There was no difference in the individual exclusion and the pooled results. However, in non-RCT studies in outcomes of thyroid weight, Randle et al. study exclusion decreases the heterogeneity and increases the sensitive analysis whereas mean operative time heterogeneity decreases to 0% when excluding Linder et al. Moreover, there is no difference in the results of estimate blood loss, thyroid vascularity and mean blood flow contributing to the sensitivity of the results which are collectively like the main results.

Asymmetry of the studies were not found in the funnel plot.

DISCUSSION:

Graves' disease is a common cause of thyrotoxicosis associated with hypervascularity [23]. A thyroidectomy in Graves' disease can be challenging due to the toxic state which increases vascularity and blood flow of the gland, increasing the risk of bleeding when compared to a non-toxic gland[24]. Various preoperative preparations have been used to reduce the vascularity and improve outcomes in operative times and ease the surgery during the operative period[25].

Lugol's Iodine was introduced in 1829 and was established as a standard preoperative treatment in Graves' disease by 1920[26]. It compromises of potassium Iodide 10% and elemental Iodine 5% with distilled water. Lugol's solution reduces the thyroid hormone by increasing the uptake of Iodine and inhibiting the enzyme peroxidase which helps in conversion of thyroid hormones in stages of oxidation and organification and block the release of the thyroid hormones. This escape of the Wolff-Chaikoff effect helps in reduction of thyroid hormone synthesis and trapping the Iodine and makes the thyroid organ less vascular and firmer, this aids the surgeon during the surgery[27].

Surgery during the hyper vascular state causes excessive bleeding and prevents from delineating the anatomy which results in an increase in morbidity and iatrogenic injury. Various attempts have been made to minimize complications by reducing the blood flow which in turn reduces the vascular density, thyroid gland weight, severity of the disease and the amount of blood loss during the surgery[14, 16].

Author	Baseline Confounding	Selection of Participants	Classification of intervention	Deviation from Intended intervention	Missing data	Measurement of outcomes	Selection of Reported Results	Overall Risk of Bias
Randle 2018	Moderate	Low	Low	Moderate	Moderate	Low	Low	Moderate
Yabuta 2009	Low	Moderate	Moderate	NI	Low	Low	Low	Moderate
Hassan 2008	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Linder 2020	Low	Low	Low	Low	Low	Low	Low	Low
Ansaldo 2000	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Huang 2015	Low	Low	Low	NI	Low	Low	Low	Low

Fig 4: ROBIN 1 quality assessment tool used for Non-RCT studies.

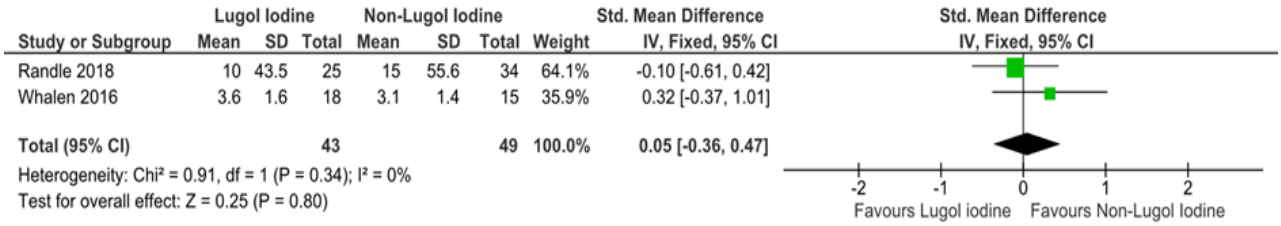
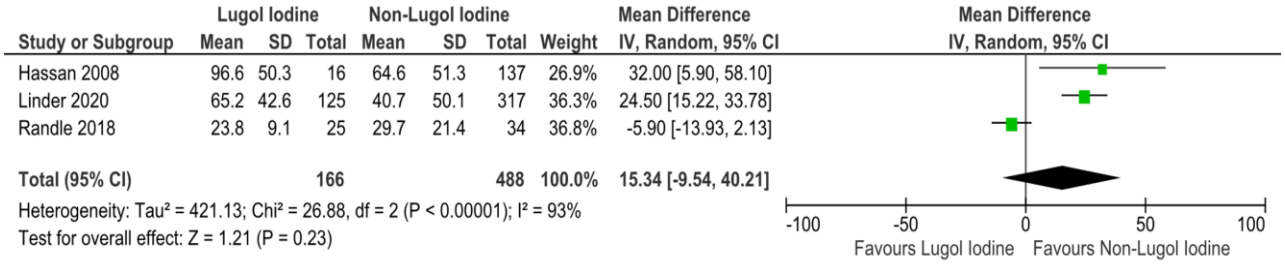


Fig 5 showing Forest plot of difficult thyroidectomy scale in Lugol Iodine versus non-Lugol's Iodine showing pooled result of 0.5% (95% CI 0.36 -0.4%)



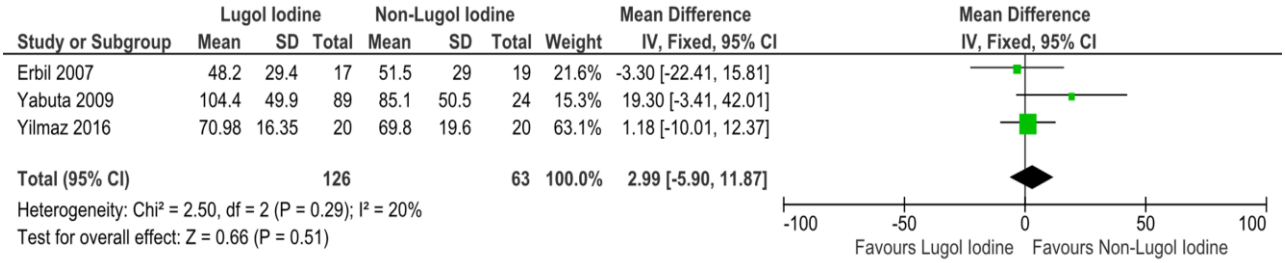


Fig 6 Showing Forest plot of Thyroid weight and volume in Lugol Iodine compared to non-Lugol's Iodine therapy with pooled results of 15.3%,2.9% (95%CI- 9.5-40%) (-5.9-11%) respectively

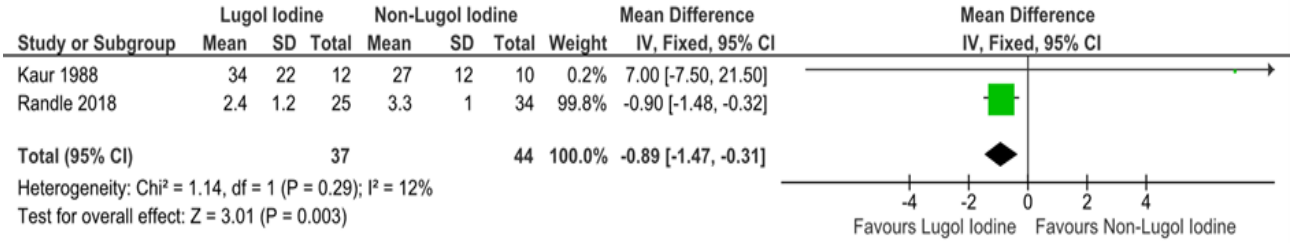


Fig 7: Forest plot of thyroid vascularity with pooled results of 0.89% (95% CI 1.4-0.3%) with heterogeneity of 12%.

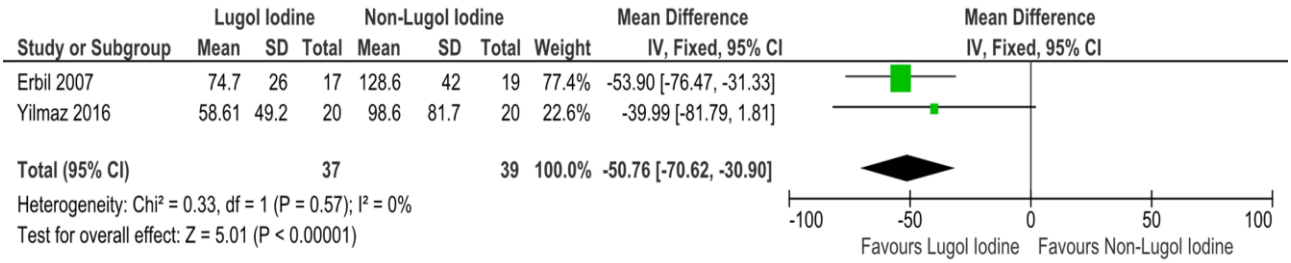


Fig 8: Forest plot with mean blood Flow with pooled result of -50% (95% CI -70- -30%)

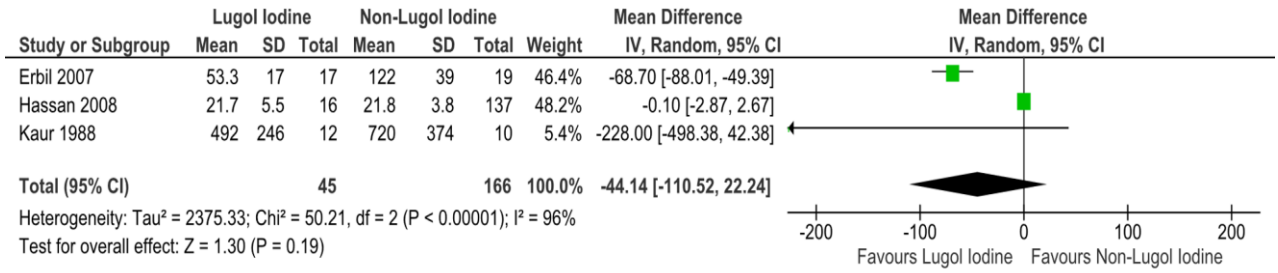


Fig 9: Forest plot of thyroid vessel density with pooled result showing -44% (95% CI -11-22%)

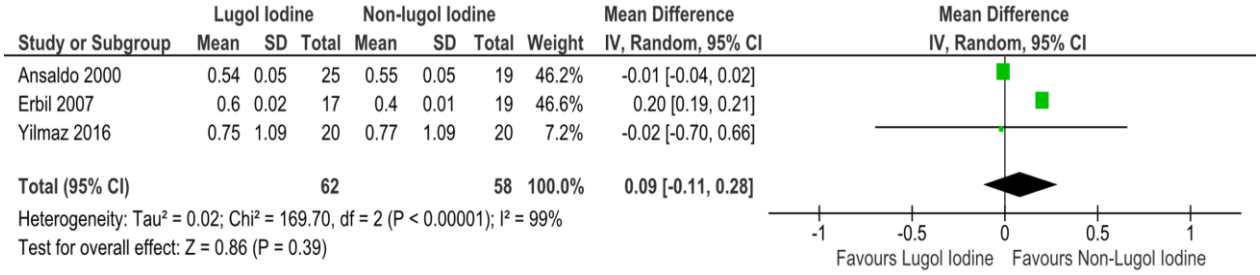


Fig 10: Forest plot showing resistance index in the vessels sampling in Lugol Iodine compared to non-Lugol's Iodine preoperatively demonstrating pooled results of 0.9% (95%CI 0.11-0.2%)

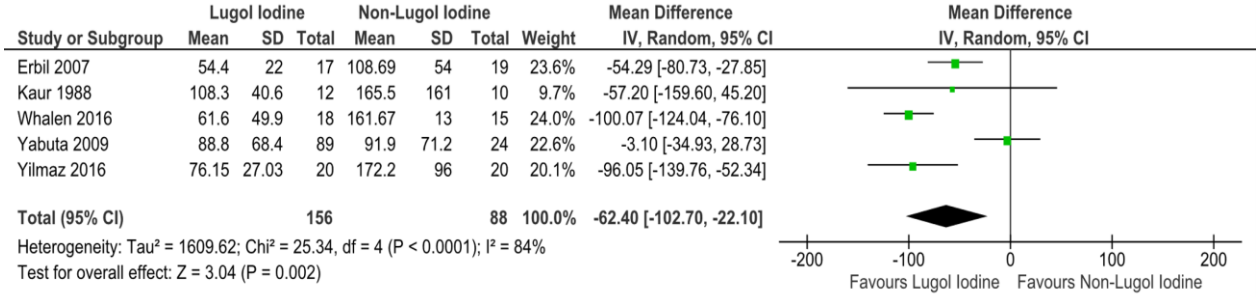


Fig 11: demonstrates estimate blood loss in both the group favouring Lugol Iodine group with pooled result of -62%(95% CI-102 to -22%)

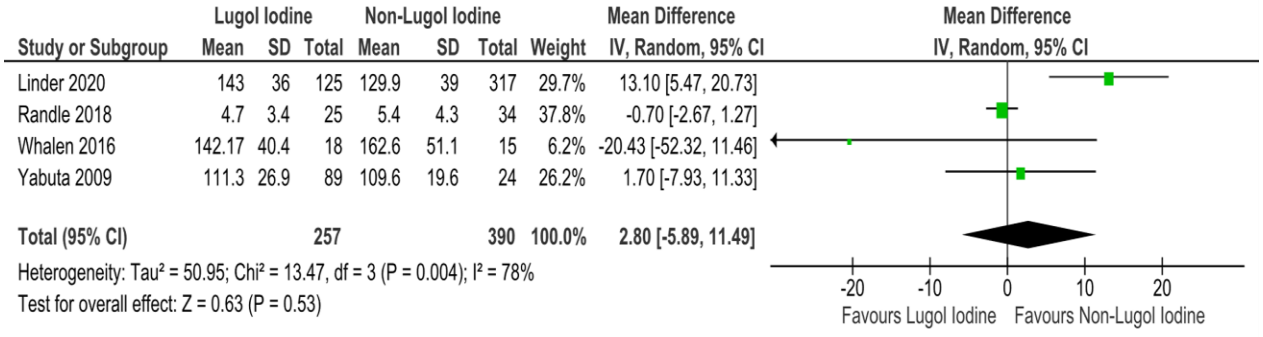


Fig 12: Forest plot of Mean operative time in both the group showing pooled result of 2%(95% CI -5.8- 11%)

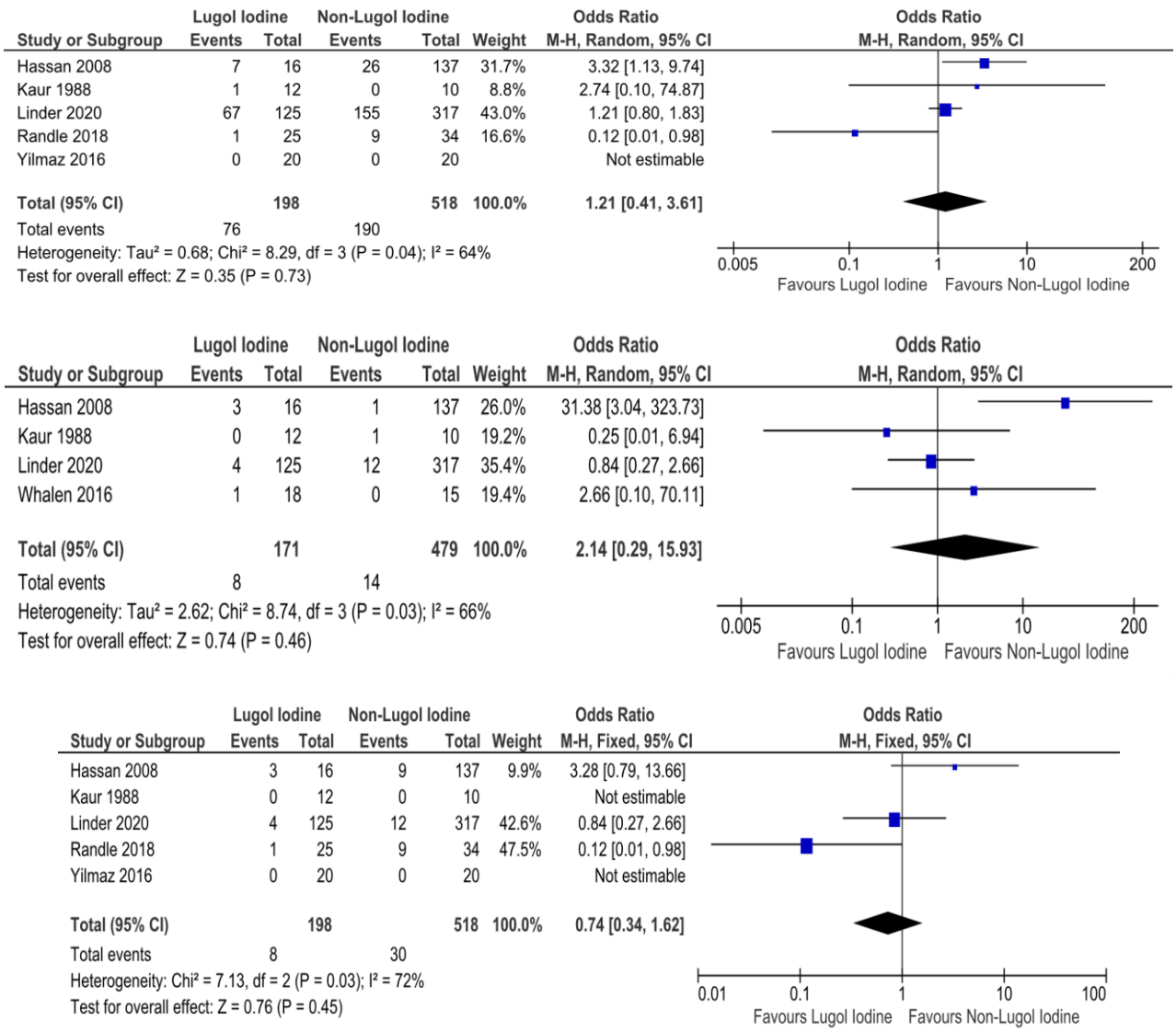


Fig 13: Forest plot showing hypocalcaemia, Vocal cord palsy and Hematoma in preoperative Lugol's Iodine compared to non Lugol's Iodine with pooled result of 1%, 2%.0.7% respectively (95% CI 0.4- 3.6%) (95% CI 0.2%-15%) (95% CI 0.3-1.6%).

During the introduction of the Lugol solution, Plummer observed decrease in mortality by 75% in Graves' disease[4] and Thomson et al[28] found it effective in inducing euthyroid state. However, the introduction of antithyroid drugs, beta-blockers and I-131, has discouraged the use of Lugol's solution, finding it inefficient to control the symptoms and hyperthyroidism in preoperative settings[7]. According to the current ATA guidelines, the use of Lugol's Iodine is recommended but its practise is on historical basis and its efficacy has not been validated. They found that, while assessing their guidelines, Lugol's solution when prescribed preoperatively offered better control in blood pressure but no differences in the heart rate, or the complication rate, even when compared to beta-blocker usage. Their analysis was restricted due to cohort studies and the size of the population as they did not have many comparisons.

We conducted this meta-analysis and added additional, most recent study conducted by Lindner[20] et al. to the previous meta-analysis to review the effect of the Lugol's Iodine in the preoperative period. We found that the vascularity of the gland is markedly decrease with the use of Lugol's solution and it causes reduction the blood flow and vascular density as a result in decrease the estimate blood losses remarkably. Huang et al.[22] in their study demonstrated a 60 % reduction in the mean blood flow from the preLugol to post Lugol state with a reduction in the serum VEGF and IL-16 level to 55% and 50% respectively. Ebril in his study depicted a reduction in the mean blood flow alongwith a reduction in vascularity and subsequent better visualization of anatomical structures which caused a reduction in intraoperative bleeding.

However, the meta-analysis found no difference in the thyroid weight, mean operative time or difference in the

postoperative complication of hypocalcaemia, injury to recurrent laryngeal nerve making the usage of Lugol's solution open to debate. Moreover, Randle et al. [17]found no difference in the thyroidectomy difficulty scale score in terms of friability, mobility, size, or fibrosis but found an increase in thyroid vascularity in patients who did not receive potassium iodide, making surgery more difficult than those who received potassium iodide. Similarly, Whalen and colleagues in their randomized control trial found similar results in the difficulty in surgery but the mean operative time and blood loss were reduced in the group which received potassium iodide preoperatively.

With the additional study including the comparison study of 442 patients to the previous meta-analysis[9] and increasing the number of participants who received preoperative Lugol's Iodine to 372 when compared to 605 who did not receive preoperative Lugol's Iodine treatment and we found the results similar and reconfirming the outcomes and benefit of receiving preoperative Lugol's Iodine in aspect to decrease in the vascularity to the gland but no additional benefit in the postoperative complications.

Linder and colleagues found increase in the operative time and thyroid weight in patient who received potassium iodide with no difference in the postoperative complication of hyperparathyroidism or recurrent laryngeal nerve injury and in postoperative bleeding. However, the meta-analysis found a decrease in hematoma formation in postoperative period in patient who received potassium iodide.

The quality of the study assessed included are randomized control trials with low risk of bias and non-randomised control trials have a strength of low reporting and selection bias with a good size of population analysed in comparison making it a reliable study. However, the study is limited in terms of variation in the strength and duration of the Lugol's Iodine given. In addition, different regimen of Iodine was given in different study. The severity of the hyperthyroidism is not mentioned in most of the study and patient who was induced euthyroid the time of remaining euthyroid was not mentioned. The duration of the antithyroid medication given or what kind of treatment received was not mentioned adds up to the weakness of the study. Moreover, the type of surgery received varies from partial, subtotal to total thyroidectomy making it a potential weakness in our meta-analysis.

CONCLUSION:

In conclusion, our meta-analysis shows that there is a significant reduction in the mean blood flow with a decrease in vascular density causing a decrease in angiogenesis in the gland, this, as a result, eases the surgeon's work owing to a decrease in vascularity and blood loss. However, there was no difference in the postoperative outcomes, operative time or difficulty in thyroidectomy scale with the use of Lugol's Iodine making it debatable if the use of Lugol's Iodine is beneficial, especially when compared to newer, and long term antithyroid medication.

ARTICLE INFORMATION Accepted for Publication: March 14, 2020
Published Online: March 30, 2020.
https://doi.org/10.48111/2020.01.02

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Financial Support and Sponsorship: Nil.

Conflicts of Interest: There are no conflicts of interest

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