

Lugol's Solution in Thyroid Surgery: A Mini-Review



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Abstract

In this mini-review the use of Lugol's solution in the preoperative management of Graves' disease is discussed, as well the underlying pathophysiological mechanisms, safety and adverse effects and clinical outcome. Special attention is given to the favourable effect of Lugol's solution on the increased blood flow, blood loss and the possible immune suppressing effect on vascular endothelial growth factor (VEGF) and the inflammatory mediator interleukine-16. In thyroidectomy for Graves' disease. It is concluded however, that the clinical relevance of Lugol's solution can not be proven and that the evidence for its use is weak. A positive effect on clinical outcome can not be demonstrated.

Conclusion: The use of Lugol's solution (LS) in thyroid surgery is now nearly a century old. LS has decreased, together with the use of the thionamides, the incidence of thyroid storm in thyroid surgery, dramatically. Blood flow and blood loss is reduced significantly by LS, probably also mediated by an immunosuppressive effect on the vascular endothelial growth factor (VEGF) and the inflammatory mediator interleukine-16 (IL-16). However the clinical relevance of this on the clinical outcome of thyroidectomy in Graves' disease can not be proven. The available literature about the need for LS in the preoperative management of Graves' disease is scanty and the level of evidence is weak. Larger, prospective, randomized, controlled trials are required to answer the question, if the use of Lugol's solution is favourable in the clinical outcome of thyroidectomy for Graves' disease.

Abbreviations: VEGF- Vascular Endothelial Growth Factor; LS- Lugol's Solution; GD- Graves' disease; CBZ- Carbimazole; MMZ- Methimazole; PTU- Propylthiouracil; TPO- Thyroid Peroxidase; FT4- Free Thyroxin; FT3- Free Thyronin; TSH- Thyroid Stimulating Hormone; DIC- Disseminated Intravascular Coagulation; ATA- American Thyroid Association

Introduction

Lugol's solution (LS) was discovered in 1829 by the French physician Jean Guillaume August Lugol. It is a solution of elemental iodine (5%), potassium iodide (10%) and distilled water. It has been used as a disinfectant, as a reagent for starch detection in organic compounds, in histologic preparations, in dental procedures and in the diagnosis of cervix alteration, also known as the Schiller's test [1]. In the 19th century LS was used, as the treatment for endemic goiter. Its use was sometimes extended to the treatment of Graves' disease, and it was in the 1930's, prior to the introduction of the thionamides, the sole treatment for mild hyperthyroidism [2]. Today, Graves' disease (GD) is common, and can be treated by medication blocking thyroid hormone synthesis, such as methimazole, carbimazole or propylthiouracil. Cure can be achieved with these drugs in 50-55% of cases, following a treatment of 12-18 months duration [3]. However, adverse effects, as agranulocytosis, hepatotoxicity, rash, arthralgias are not uncommon. The choice for an antithyroid drug in GD in pregnancy is a difficult one.

There is increasing evidence for a carbimazole/methimazole (CBZ/MMZ) embryopathy, whilst data for major congenital abnormalities with propylthiouracil (PTU) are lacking [4]. Treatment of GD in pregnancy with LS for thyroid surgery could be an option, in cases of intolerance for antithyroid drug therapy [5]. When intolerance for antithyroid drugs is present, and radioiodine therapy is contraindicated, LS can be used in preparation of thyroid surgery for GD [5]. Surgery is much safer, when the patient is euthyroid. In untreated thyrotoxicosis the frequency of bleeding, due to the high vascularization of the thyroid, and anaesthetic complications are believed to be higher, compared to euthyroid patients [6]. In this mini-review the use of LS in thyroid surgery, underlying mechanisms, safety and adverse effects, and clinical outcomes will be discussed.

Mechanisms of "Plummering":

Preparing a patient with LS for elective thyroid surgery in hyperthyroidism, is frequently called "Plummering", named after Dr Henry S Plummer, who used LS in the treatment of a toxic

exophthalmic goiter patient in 1924 [2,7]. His demonstration, that preoperative administration of LS made surgery of severe exophthalmic goiter a safe procedure with a surgical mortality less than 1%, has saved countless lives [8]. "Plummering" is based on the acute Wolff-Chaikoff effect, referring to the inhibitory effect of excess iodide on thyroid hormones synthesis [8,9]. As in LS administration, excess iodine is transported into the thyroid gland by the sodium-iodide transporter. This transport results in a transient inhibition of thyroid peroxidase (TPO) and a decrease in the synthesis of thyroid hormones, within 24-48 hours. Thereafter, following a decrease in the expression of the sodium-iodide transporter, it results in reduced iodine transport, which enables the thyroid hormone production to resume.

This "escape Wolff-Chaikow" effect results from down-regulation of the sodium iodine symporter, through activation of the phosphatidylinositol-3 kinase protein kinase B pathway, by acute iodide exposure [10]. This results in a decrease in intrathyroid iodide concentration. LS is administered during 10 days, 0, 5 ml or 375 mg daily. Free thyroxin (FT4) and free thyronin (FT3) are significantly reduced within 5-10 days, whilst thyroid stimulating hormone (TSH) remains undetectable [11]. Prolonged use of LS (30 days) can result in severe hyperthyroidism, due to the Jod-Basedow effect [12]. The patient should attain euthyroid status before the surgery and this should be confirmed by normalization of the thyroid function tests, especially free thyroxin (FT4) [13,14].

Effect of LS on intraoperative bleeding:

Yilmaz et al. randomly assigned 40 euthyroid patients on antithyroid drugs, who admitted for surgery, due to hyperthyroidism to LS pretreatment or no LS pretreatment. The control group consisted of 10 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, T4, TSH and thyroid volume and the resistance index of the 4 main thyroid arteries were measured in all patients. The LS group and non-LS group did not differ in serum thyroid hormone values or thyroid gland volumes. The mean blood flow was significantly lower in the LS group, compared to the non-LS group. When age, gender, serum thyroid hormone levels, thyroid volume and LS treatment were included, as independent variables, LS treatment (OR, 7, 40; 95% CI, 1, 02-58, 46; $p=0,001$) was found to be the only significant determinant of intraoperative blood loss. LS treatment resulted in a 7,4 fold decrease in intraoperative blood loss [15].

In a small prospective multicenter trial (n=36) Erbil et al. [16] assigned 36 GD patients on antithyroid drugs, to receive either preoperative treatment with LS (n=17) and no LS treatment (n=19). Blood flow through the thyroid arteries was measured by color flow Doppler ultrasonography. Microvessel density was measured by immunohistochemical expression of CD-34 in thyroid tissue. The weight and blood loss of the thyroid gland

were measured in all patients. Mean blood flow, microvascular density and blood loss were significantly lower in the LS group. After logistic regression Lugol solution treatment resulted in a 9,33 fold decreased rates of intraoperative blood loss. Other studies measured thyroid blood flow by Thallium-201 uptake. In a small study (n=9) Marigold concluded, that thyroid blood flow is reduced in thyrotoxic patients treated with LS [16].

Huang et al. [17] measured the blood flow through the superior thyroid arteries by color Doppler ultrasonography, in patients with GD on antithyroid drugs and/or beta-blockers. (n=33). Blood loss was measured by the suction bottle and the weight of the thyroid gland was measured. Microvessel density was measured by Factor 8 expression in thyroid tissue. They concluded, that preoperative color flow Doppler ultrasonography may help in identifying patients with Graves' disease, who are liable to bleed intraoperatively during thyroidectomy. Ten patients having a blood loss exceeding 200 ml during thyroidectomy showed a higher preoperative blood flow ($p<0,001$) Diffuse microfollicular hyperplastic thyroid tissue had a significantly higher blood flow and vascular density, than tissue with an inactive colloid pattern ($p<0,001$) [17]. The rationale for the effect of LS on blood flow and blood loss during thyroid, is believed to be related to its effect on the vascular endothelial growth factor (VEGF) and the systemic immune inflammatory mediator interleukin-16 (IL-16).

In a small study (n=25) patients with euthyroid GD were treated with LS preoperatively for 10 days and measured at baseline and on the operative day for superior thyroid arterial blood flow, VEGF and IL-16 levels. All three parameters were significantly lower after 10 days LS treatment. The average reduction in blood flow was 60%, in serum VEGF levels 55%, and 50% in IL-16 levels. For this reason the authors recommend LS treatment for all GD patients, including those, who are euthyroid already [18]. This view is not shared from an ENT surgeon standpoint as Santosh et al stated [19].

LS in thyroid storm

Thyroid storm is most commonly associated with underlying Graves' disease. The condition was frequently encountered following thyroidectomy for thyrotoxicosis, due to manipulation of the hyperactive gland during surgery, but modern treatment with antithyroid drugs, and/or beta-blockers have dramatically reduced this complication. While in former days the mortality was nearly 100%, it is still a serious condition. The incidence is less than 10% in patients hospitalized now, but mortality rate is still 20-30%. Nowadays it occurs more in hyperthyroidism, complicated by a precipitating event as an infection, myocardial infarction, diabetic keto-acidosis [20]. Thyroid storm is defined as extreme thyrotoxicosis with fever, tachycardia, congestive heart failure and gastrointestinal/hepatic disturbances [20,21].

In elderly patients a total apathetic state can be present [22]. Mortality is mostly due to multiorgan failure with

disseminated intravascular coagulation (DIC), congestive heart failure, respiratory failure, abdominal perforations and sepsis [23]. Treatment is directed at supportive care, inhibition of new hormone synthesis and release, peripheral beta-adrenergic blockade, preventing conversion from T4 to T3 and identifying precipitating factors [21,23]. Fluid losses, resulting from fever, diaphoresis, vomiting and diarrhea should be replaced. Thionamides inhibit synthesis of thyroid hormones by preventing organification and trapping of iodide to iodine and by inhibiting coupling of iodotyrosines [24].

Methimazole has a longer half-life time than PTU, permitting less frequent dosing. It presents in free form in the serum, whereas 80-90% of PTU is bound to albumin. The dose for methimazole is 40-100 mg given orally or by nasogastric tube, followed by 20 mg every 4 hours, until a 120 mg dose daily. If given rectally the dose is 40 mg, crushed in an aqueous solution. Methimazole can be given intravenously too. Carbimazole is the prodrug for methimazole and can be given as a loading dose of 40-60 mg, followed by a maintenance dose of 5-20 mg daily.

As for PTU, the dose for thyroid storm is 600-1000mg given orally, as a loading dose, followed by 200-250 mg every 4 hours. The total daily dose is between 1200-1500 mg daily. PTU inhibits also the conversion of T4 to T3. Lugol's solution can be given to stop hormone release 1 hour after starting with thionamides. LS can be given 3-4 times/day to a total of 20-40 drops/daily. Each Lugol drop provides 8 mg iodide. The peripheral conversion of T4 to T3 is blocked by PTU, propranolol and glucocorticoids. The blocking effect of PTU and propranolol is quantitatively not significant, so glucocorticoids, as hydrocortisone, dexamethasone are essential in the treatment of thyroid storm. A vigorous search for precipitating factors should be performed.

Safety and adverse effects of LS

Hypersensitivity is the most common side effect ranging from 1-15% in some patient groups. Other adverse effects are sialadenitis, and gastrointestinal disturbances [25]. Anaphylactoid reactions are rare [26]. It has been reported, that with prolonged use, hyperthyroidism develops after 21 days [27]. However, in Japan, long-term treatment with iodine has been used alone or together with antithyroid drugs, to achieve euthyroidism, with good results [28].

Clinical outcomes in LS use:

The American Thyroid Association (ATA) recommends 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 postoperative period [29]. In a recent review by Hope and Kelly, the levels of evidence for these guidelines are weak, based on the available literature [30]. Reduced blood flow and blood loss, during thyroidectomy, might be attractive for any surgeon, but the clinical relevance is somewhat lacking. Furthermore, the surgical issues, how

to handle, when thyroid storm occurs during surgery, are not available [31]. None of the 4 eligible studies reviewed, report whether or not, there were any adverse effects of taking iodine in the preoperative period, and there is no mention of the incidence of adverse outcomes in the hyperthyroidism patients, for whom surgery was delayed [32].

Conclusion

In addition, the heterogeneity of the groups studied was considerable, not only in individual papers, but also between them, containing GD as toxic multinodular goiter patients as well. The indications for surgery differed enormously. The authors conclude, this reduces the ability to answer the question of the need for iodine solution in the preoperative period for any given condition, and it makes a further comparison with other trials difficult. Larger, prospective, randomized, controlled trials are required to answer, whether or not preparation with Lugol's solution is in fact necessary prior to surgical intervention for Graves' disease [32].

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