

# Rapid Preparation of Hyperthyroid Patients for Thyroidectomy

## Hipertiroid Hastaların Tiroidektomiye Kısa Zamanda Hazırlanması

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**ABSTRACT Objective:** Preoperative preparation of hyperthyroid patients is extremely important to avoid complications due to severe thyrotoxicosis during surgery. We investigated the effects of lugol's solution (LS) with or without thionamides in the rapid preparation of the patients for thyroid surgery and compared the effect of LS in patients with Graves' disease (GD) and toxic multinodular goiter (TMNG). **Material and Methods:** Data were collected retrospectively from 44 patients with hyperthyroidism who were followed up in our clinic. Twenty-two patients with GD, 19 patients with TMNG and three patients with solitary toxic adenoma were enrolled into the study. To restore euthyroidism before surgery, 27 patients were treated with LS (group 1) while 17 patients received LS and thionamides (group 2). **Results:** Mean daily total dosage of LS and duration of treatment to restore euthyroidism were not statistically different between groups 1 and 2. When the two treatment groups were compared, there was no significant difference in baseline parameters and percentage of changes of serum fT4 and fT3 levels. Duration of LS treatment and dosages of LS and thionamides were also similar in patients with GD and TMNG. Percentage of changes in serum fT4 and fT3 levels after LS treatment were not statistically different in two groups of patients. All patients were clinically euthyroid before surgery. **Conclusion:** LS treatment, either alone or together with antithyroid drugs, is a safe and effective choice for the rapid preparation of hyperthyroid patients for thyroidectomy, independent from the etiology of hyperthyroidism.

**Key Words:** Hyperthyroidism; thyroidectomy; lugol's solution

**ÖZET Amaç:** Hipertiroid hastaların preoperatif hazırlığı ağır tirotoksikozaya bağlı preoperatif komplikasyonlardan kaçınılmede çok önemlidir. Tiroid cerrahisine kısa zamanda hazırlık yapılabilmesinde lugol solüsyonunun (LS) tiamidlerle veya yalnız başına etkilerini araştırmak ve LS'nin Graves hastalığı (GD) olanlarda ve toksik multinodüler guatrli (TMNG) olgulardaki etkilerini karşılaştırdık. **Gereç ve Yöntemler:** Kliniğimizdeki hipertiroidizimli 44 olgunun verileri retrospektif olarak değerlendirildi. GD'li 22 olgu, TMNG'li 19 olgu ve soliter toksik adenomlu üç olgu çalışmaya alındı. Cerrahiden önce ötiroidizm sağlamak için 27 olgu LS ile (grup 1) tedavi edilmişti, 17 olgu LS ve tiamid almıştı (grup 2). **Bulgular:** Alınan ortalama günlük total LS dozu ve ötiroidizm sağlamak için geçen tedavi süresi grup 1 ve grup 2 arasında istatistiksel olarak farklılık göstermiyordu. İki tedavi grubu karşılaştırıldığında temel parametrelerde ve serum FT4 ve FT3 düzeylerinin yüzdelerindeki değişiklik yönünden fark yoktu. LS tedavi süresi ve LS ve tiamid dozları GD ve TMNG olgularında benzerdi. LS tedavisinden sonraki serum FT4 ve FT3 düzeylerindeki yüzde değişiklikleri her iki hasta grubunda istatistiksel olarak farklı değildi. Bütün hastalar cerrahiden önce klinik olarak ötiroid durumdaydı. **Sonuç:** Tek başına veya antitiroid ilaçlarla birlikte uygulanan LS tedavisi altta yatan hipertiroidizm etyolojisinden bağımsız olarak hipertiroid hastaların tiroidektomi için kısa zamanda hazırlanabilmesinde güvenli ve etkili bir seçenektir.

**Anahtar Kelimeler:** Hipertiroidizm; tiroidektomi; lugol solüsyonu

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Thyroidectomy is an alternative treatment in the therapy of hyperthyroidism in patients who are non-compliant or drug-resistant or who have various side effects to the antithyroid drugs. Preoperative thyrotoxicosis is a potentially life-threatening condition that requires medical intervention before surgery. The goal of therapy is to render the patient as fast as possible to clinical and biochemical euthyroidism before surgery.<sup>1,2</sup> Thionamides are the preferred initial treatment to restore euthyroidism in hyperthyroid patients if they do not cause side effects such as pancytopenia, hepatotoxicity or allergic reactions. However, it can take several weeks to achieve euthyroid status with these drugs.<sup>3</sup> Other agents, including steroids and beta-blockers, can be used with or without thionamides if more severe thyrotoxicosis is present, or if rapid preparation is needed.<sup>4,5</sup> Iodine therapy can also be used for rapid restoration of euthyroidism in such patients, either together with thionamides or alone, if thionamides are contraindicated.<sup>6</sup> Pharmacologic amounts of iodine ameliorate hyperthyroidism by blocking thyroid hormone release and temporarily inhibiting iodine organification in the thyroid gland.<sup>7-10</sup> Published regimens for rapid preparation for surgery include iodine-rich oral radiographic contrast agents (IRCA) such as sodium ipodate, which are no longer available in most European countries.<sup>8,9,11,12</sup> Lugol's solution (LS) (8 mg iodide/drop) and saturated solution of potassium iodide (SSKI) (40 mg iodide/drop) are the other options available for use as an iodide donor.<sup>13-16</sup>

In the present study, we aimed to investigate the effects of LS used alone or together with thionamides for the rapid preparation of hyperthyroid patients for thyroid surgery. In addition, we compared the effects of LS in hyperthyroid patients with Graves' disease (GD) and toxic multinodular goiter (TMNG).

## MATERIAL AND METHODS:

A retrospective analysis of hyperthyroid patients treated with LS for restoration of euthyroid state before thyroidectomy was performed following ethical guidelines. Twenty-two patients with GD, 19 patients with toxic multinodular goiter (TMNG) and three patients with solitary toxic adenoma who

were diagnosed and followed up in our clinic between 2004 and 2008 were enrolled in the study. We documented demographic and clinical data for each patient including age at the time of treatment, gender, and clinical and scintigraphic work up. We also recorded thyroid functions and thyroid antibody levels.

The criteria for hyperthyroidism included presence of clinical symptoms, increased serum concentrations of free thyroxine (fT4), increased free triiodothyronine (fT3) and decreased basal thyrotropin (TSH) levels. The criteria for GD were based on initially documented hyperthyroidism with or without ophthalmopathy, increased uptake in the technetium scintigraphy and the presence of positive thyroid antibodies. TMNG and solitary toxic adenoma were diagnosed if the uptake was patchy with multiple areas of increased uptake or confined to a single hot area associated with biochemical hyperthyroidism, respectively.

Serum fT3, fT4 and TSH concentrations were measured by automated luminescent immunoassays (Abbott Laboratories, Abbott Park, USA). The mean coefficient of variation was below 10% for all of these assays. The normal ranges for thyroid function tests were as follows: fT3: 1.71-3.71 pg/ml; fT4: 0.7-1.48 ng/dl; and TSH: 0.35-4.94 mIU/ml.

Data were presented as means with standard deviations or percentages where appropriate.  $X^2$  test was used for clinical variables. Student t and Mann-Whitney U tests were used to assess the differences between groups. The data were analyzed using SPSS for Windows, version 11.5. A p value less than 0.05 was considered as statistically significant.

## RESULTS

A total of 44 patients were included in the study. The mean age of patients was  $46.6 \pm 14.7$  years and mean duration of hyperthyroidism was  $38.2 \pm 59.3$  months. The indications for surgery were as follows: No-response to medical treatment (n= 19), pancytopenia (n= 9), hepatotoxicity (n= 6), allergic reactions (n=3), and non-compliance (n=7) with thionamides. Thirty-six patients were using propylthiouracil and eight patients were using methimazole when surgery was planned. Frequency of

pancytopenia and hepatotoxicity as well as serum AST and ALT levels were not statistically different in patients using propylthiouracil when compared to patients using methimazole.

To restore euthyroidism before surgery, 27 patients were treated with LS (group 1) while 17 patients received LS and thionamides (group 2). Baseline characteristics of patients and laboratory findings in two groups are summarized in Table 1. There was no statistically significant difference for baseline parameters between two groups. In group 2, propylthiouracil (n= 12) and methimazole (n= 5) were used as thionamides obtain euthyroidism before surgery. Mean dosages of propylthiouracil and methimazole were  $413 \pm 221.4$  and  $28.3 \pm 10.3$  mg, respectively.  $\beta$ -blockers were used in 20 patients of group 1 and in 11 patients of group 2. None of the patients were treated with corticosteroids (Table 2).

LS was given three times a day by dividing the total daily dose. Mean total daily dose of LS was  $29.0 \pm 3.4$  drops ( $232.0 \pm 27.2$  mg) and mean duration of treatment to restore euthyroidism was  $10.1 \pm 1.8$  (range: 6-14) days in group 1 while these values were  $25.5 \pm 7.4$  drops ( $204.0 \pm 59.2$  mg) and 9.0

$\pm 2.8$  (range: 5-13) days respectively in group 2. Mean daily total dose of LS and mean duration of treatment to restore euthyroidism were not statistically different in two groups. No side effects were seen due to the use of LS in either groups. After Lugol's solution treatment (LT), serum fT4 concentration decreased from  $2.7 \pm 1.9$  to  $1.4 \pm 0.7$  ng/dl in group 1 and from  $2.2 \pm 0.9$  to  $1.2 \pm 0.6$  ng/dl in group 2, whereas serum fT3 concentration decreased from  $11.3 \pm 8.0$  to  $4.3 \pm 4.6$  pg/ml in group 1 and from  $8.0 \pm 5.7$  to  $3.0 \pm 0.8$  pg/ml in group 2. There were no differences in percentage changes in serum fT4 and fT3 when the two treatment groups were compared (Table 2). We also compared clinical characteristics and laboratory findings of patients with GD and TMNG before and after treatment with LS. Patients with TMNG were older and had higher serum fT3 levels compared to patients with GD ( $p= 0.005$  and  $p= 0.003$ , respectively). Serum mean fT4 and fT3 levels and percentage changes in serum fT4 and fT3 levels after LT were comparable in patients with GD and TMNG. There were no other statistically significant differences between the two groups, including duration of LT and doses of thionamides and LS (Table 3).

**TABLE 1:** Baseline patient characteristics and laboratory findings in two groups.

	Group 1	Group 2	p
n (male/female)	27 (3/24)	17 (5/12)	NS
Mean age (years)	$47.0 \pm 13.8$	$46.0 \pm 16.5$	NS
Mean duration of hyperthyroidism (months)	$34.1 \pm 55.9$	$44.8 \pm 65.7$	NS
Mean duration of thionamide use before LT (months)	$14.4 \pm 17.8$	$16.3 \pm 19.1$	NS
Type of used thionamides before LT (n)			
Propylthiouracil	25	11	0.04
Methimazole	2	6	
Mean dose of thionamides before LT (mg)			
Propylthiouracil	$300.0 \pm 170.1$	$400.0 \pm 213.0$	NS
Methimazole	$35.0 \pm 35.0$	$26.6 \pm 10.0$	NS
Etiology of hyperthyroidism (n)			
Graves' disease	14	8	
Toxic multinodular goiter	10	9	NS
Solitary toxic adenoma	3	0	
Mean serum TSH level before LT (mIU/ml)	$0.01 \pm 0.02$	$0.05 \pm 0.13$	NS
Mean serum fT4 level before LT (ng/dl)	$2.7 \pm 1.9$	$2.2 \pm 0.9$	NS
Mean serum fT3 level before LT (pg/ml)	$11.3 \pm 8.0$	$8.0 \pm 5.7$	NS

Group 1= patients using Lugol's solution alone, group 2= patients using Lugol's solution and thionamides, LT= Lugol's solution, TSH= thyrotropin, fT4= free thyroxine, fT3=free triiodothyronine.

**TABLE 2:** Serum thyroid hormone levels after treatment.

	Group 1 (n= 27)	Group 2 (n= 17)	p
No of patients using propylthiouracil/methimazole	-	12/5	-
Mean dose of propylthiouracil/methimazole (mg)	-	413.6 ± 221.4/28.3 ± 10.3	-
Mean dose of LT (drops) (mg)	29.0 ± 3.4 (232.0 ± 27.2)	25.5 ± 7.4 (204.0 ± 59.2)	NS
Mean duration of LT (days) (range)	10.1 ± 1.8 (6-14)	9.0 ± 2.8 (5-13)	NS
Patients using β-blockers (n) (%)	20 (74%)	11(64%)	NS
Mean serum TSH after LT (mIU/ml)	0.06 ± 0.27	0.10 ± 0.22	NS
Mean serum fT4 after LT (ng/dl)	1.4 ± 0.7	1.2 ± 0.6	NS
Mean serum fT3 after LT (pg/ml)	4.3 ± 4.6	3.0 ± 0.8	NS
Δ change in serum fT4	-34.3 ± 36.8	-42.4 ± 25.1	NS
Δ change in serum fT3	-52.8 ± 26.3	-48.6 ± 27.8	NS

Group 1= patients using Lugol's solution treatment alone, group 2= patients using Lugol's solution and thionamides, LT= Lugol's solution treatment, TSH= thyrotropin, fT4= free thyroxine, fT3=free triiodothyronine, NS=not significant.

**TABLE 3:** Characteristics and laboratory findings of patients with Graves' disease and toxic multinodular goiter.

	Patients with GD (n= 22)	Patients with TMNG (n= 19)	p
Gender (male/female)	5/17	3/16	NS
Age (years)	40.6 ± 10.8	55.7 ± 14.4	0.001
Duration of hyperthyroidism (months)	25.9 ± 47.3	55.1 ± 71.7	NS
Mean serum TSH before LT (mIU/ml)	0.02 ± 0.05	0.03 ± 0.10	NS
Mean serum fT4 before LT (ng/dl)	2.9 ± 2.2	2.1 ± 0.6	NS
Mean serum fT3 before LT (pg/ml)	13.2 ± 8.6	6.8 ± 4.3	0.005
Patients treated with LT alone (n)	14 (63.6%)	10 (52.6%)	NS
Patients treated with LT and thionamides (n)	8 (36.3%)	9 (40.9%)	NS
Mean duration of LT (days)	9.4 ± 1.9	10.0 ± 2.6	NS
Mean dosage of Lugol's solution (drops) (mg)	28.8 ± 3.7 (230.4 ± 29.6)	27.3 ± 6.5 (218.4 ± 52.0)	NS
Usage of β-blockers (n)	18 (81.8%)	11 (57.9%)	NS
Mean dosage of propylthiouracil (mg)	475.0 ± 250	378.5 ± 215.7	NS
Mean dosage of methimazole (mg)	27.5 ± 13.2	30.0 ± 0.00	NS
Δ change in serum fT4	-38.6 ± 40.4	-32.7 ± 23.6	NS
Δ change in serum fT3	-57.4 ± 29.0	-41.5 ± 22.1	NS

GD= Graves' disease, TMNG= toxic multinodular goiter, LT= Lugol's solution treatment, TSH= thyrotropin, fT4= free thyroxine, fT3=free triiodothyronine, NS=not significant.

All patients were in clinically euthyroid before surgery. Uneventful total or subtotal thyroidectomies were performed in 37 patients and a hemithyroidectomy was performed in seven patients.

## DISCUSSION

In the present study, we demonstrated that LT, alone or together with thionamides, was safe and effective for the rapid preparation of hyperthyroid

patients for thyroidectomy. We also investigated whether there were any differences in the effects of LS on thyroid hormone levels in patients with GD or TMNG, since the etiology of hyperthyroidism is different in these two diseases, however no statistically significant difference was detected.

Preoperative preparation of patients with hyperthyroidism is important to avoid the deleterious effects of thyrotoxicosis on heart rhythm at the

time of surgery and to reduce intraoperative and postoperative complications. Euthyroid state can be accomplished with the administration of thionamides, but the treatment usually takes months.<sup>3,19</sup> Rapid and safer control of thyrotoxicosis can be achieved with oral administration of iodide in combination with thionamides or with iodide alone, if thionamides are contraindicated.<sup>8-12</sup> In pharmacological doses, the major action of iodides is to inhibit hormone release, possibly through inhibition of thyroglobulin proteolysis.<sup>10</sup> Rapid improvement occurs in thyrotoxic symptoms within 2-7 days with iodide therapy.<sup>7</sup>  $\beta$ -blockers and corticosteroids can be used to inhibit the conversion of fT4 to fT3 and to decrease the peripheral effects of thyroid hormones when of urgent surgery is needed.<sup>4,5</sup>

IRCA, SSKI and LS are available iodide donors. It has been reported that IRCAs such as sodium ipodate and iopanoic acid (IOP) are more effective in the rapid restoration of euthyroidism when compared to SSKI which contains more iodine per drop compared to LS.<sup>14-16</sup> IRCAs have multiple actions on thyroid hormone metabolism. They competitively inhibit the conversion fT4 to fT3 in the brain, liver, kidney and pituitary gland and also inhibit thyroid hormone secretion from the gland.<sup>7</sup> Panzer et al. reported that in the majority of patients with GD, total T3 levels had returned to the normal range after a 4-day treatment with IOP, and all of their patients had surgery after a mean treatment duration of 7 days.<sup>8</sup> They also found that serum T4 levels decreased far less than serum T3 concentrations, probably due to decreased plasma clearance of T4 during IOP use. In the present study, the minimum time to accomplish normal thyroid hormone levels was five days, whereas the mean duration with LT was  $9.7 \pm 2.3$  days. In Baeza et al.'s study, serum T3 levels had diminished by  $64.5 \pm 16.6\%$  on the sixth day of treatment and serum T4 concentration showed a slight but significant decrement only from day 4 on and the patients never reached euthyroid levels with IOP.<sup>9</sup> Decrements in serum T3 seen in Panzer et al.'s and Baeza et al.'s studies were more prominent compared to our results.<sup>8,9</sup> This may be attributed in part to the use of corticosteroids in both of those studies,

since corticosteroids inhibit the conversion of T4 to T3. Corticosteroids were not used for the rapid preparation of patients for thyroid surgery in the present study. While Panzer et al. assessed serum total T4, T3 and fT4 index and Baeza et al. assessed total T4, T3 and reverse T3, we measured serum fT3 and fT4 levels, since they more correctly reflect the thyroid hormone status of patients.<sup>3,8,9,16</sup> However, the major difference between IRCAs and LS appears to be the time required for restoration of euthyroidism, which is shorter with IRCAs, whereas decrements in serum fT4 levels are greater with LS.

The use of iodide therapy without thionamides is not recommended if thionamides are not contraindicated because the effects of iodide block disappears in 2-8 weeks.<sup>7,17,20,21</sup> Kaur et al. reported in their study that over one-third of patients with GD had subnormal levels of thyroid hormones at the time of surgery operation when antithyroid drugs were stopped 10 days before partial thyroidectomy, and patients were treated with LS alone.<sup>18</sup> In the present study, LS was used without thionamides in 27 patients who had various side effects due to thionamides. Nevertheless, the percentage changes in serum fT4 and fT3 levels showed no significant differences between the two treatment groups. Adverse reactions such as acneiform rash, swollen salivary glands, mucous membrane ulcerations, and rarely anaphylactoid reactions can be observed with the use of iodines.<sup>3,7</sup> However, no adverse reactions developed in our patient population and LS was well tolerated.

In conclusion, these results suggest that LS is an effective and safe therapeutic option when used alone or together with thionamides for the rapid preparation of hyperthyroid patients for thyroidectomy, independent of the etiology of hyperthyroidism.

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