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Preoperative Preparation of Hyperthyroidism for Thyroidectomy – Role of Supersaturated Iodine and Lithium Carbonate

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Abstract

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Introduction:

Thyroidectomy is effective and safe procedure for permanent cure of hyperthyroidism (HT). Iodine preparations are widely used before operation to prevent excess blood loss. Ideal regimen for refractory HT is debated. This retrospective case–control study is designed to study the efficacy of various regimens of preoperative preparations.

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Materials and Methods:

Case records, anesthesia charts, and follow-up details of hyperthyroid patients undergoing thyroidectomy were reviewed and compared with an age- and sex-matched euthyroid patients operated during the same period. Iodine preparations were not used for preoperative preparation. Study group was subdivided based on preoperative regimens of anti-thyroid medications.

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Results:

Of the 168 patients in the study group, procedure time, duration of hospital stay, and overall complication rate were high compared to euthyroid group. Operative blood loss was not high in the study group. There was no difference in rate of complications in the subgroups of the study cohort.

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Conclusion:

Iodine preparations are not mandatory in preoperative preparation of HT. Lithium carbonate is effective in preoperative preparation of refractory HT. Rate of postthyroidectomy complications is not different in patients receiving thionamides alone or in combination with β-blocker.

Keywords: Graves' disease, lithium carbonate, Lugol's iodine, total thyroidectomy

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Introduction

Thyroidectomy is offered as definitive treatment for overt hyperthyroidism (HT) in selected patients. In general, patients with large volume goiter, pressure effects, suspicion of malignancy, advanced orbitopathy, and recurrence following repeated I^{131} therapy are considered candidates for thyroidectomy. Adequate preoperative preparation reduces chances of intraoperative and immediate postoperative adverse events. Thionamides and β-blockers are first-line drugs used, but the latter is occasionally withdrawn when symptoms subside. Cardiovascular effects of excess thyroxine predispose patients to develop supraventricular arrhythmias during thyroidectomy and immediate postoperative period. B-adrenergic blockade averts such possible deleterious effects. Propranolol in high doses (above 160 mg/day) also inhibits 5'-monodeiodinase and thereby decreases serum triiodothyronine (T3) concentrations.

Supersaturated iodine (SSI) preparations are widely recommended before thyroidectomy in an attempt to reduce vascularity of the gland.[1] Complete mechanism for the acute Wolff–Chaikoff effect is not fully understood but is thought to be due to the generation of several inhibitory substances acting on thyroid peroxidase activity. In general, the decreased production of thyroid hormones is only transient and resumes after adaptation.[2,3] Thyroid blood flow was found reduced in experimental rats fed on high dose of iodine by 56% and 46% on day 7 and 14, respectively.[4] The effect of SSI on thyroid function and blood flow seems to be transient, and escape phenomenon is not uncommon. Paradoxically persistent failure to adapt to Wolff–Chaikoff effect was observed in certain susceptible patients who received long term medications for autoimmune thyroid diseases and those who received I^{131} ablation.[3] There is an increasing recognition of thyroid cancers among patients with Graves' disease (GD). Recent collective review showed 10%–15% nodule prevalence in GD with 2.3%–45.8% (mean 16.9%) risk of malignancy.[5] Problems related to SSI usage include significant rate of poor response or even exacerbation and delay in I^{131} therapy when thyroid cancer coexists. The endocrine surgery division was not using SSI for the past 15 years since the senior author, who used it earlier, was not convinced with its beneficiary effects.

Occasional patients require alternative regimen for preoperative preparation when routine antithyroid medications are ineffective or contraindicated. Options for such patients are SSI, plasmapheresis, lithium, and cholestyramine. Conventionally, iodine preparations along with β-blockers were used in such situations. However, many SSI preparations are no longer universally available and so we resorted to lithium carbonate as an alternative. Lithium is concentrated by the follicular cells and inhibits thyroidal iodine uptake and iodotyrosine coupling, alters thyroglobulin structure, and thereby inhibits thyroid hormone secretion.[6] There are anecdotal reports in literature showing the efficacy of lithium in such circumstances.[7,8] Given the uncertainty of SSI regarding complete prevention of iodine leak and considering the iodine as a substrate of thyroxine synthesis, lithium salt may be preferred agent. Untoward effects of lithium are rare when serum level is maintained between 0.6 and 1.0 mEq/L whereas levels >1.2 mEq/L can lead to toxicity. The desired serum levels are achieved with tablet strength of 300–600 mg three times daily.[9,10] Dexamethasone even at a low dose can modulate thyroid-stimulating hormone (TSH) level and inhibits the5-deiodinase.[11] We had used combination of lithium carbonate and dexamethasone in refractory HT as preoperative regimen.

This retrospective case–control study was done in patients who underwent thyroidectomy for HT during 2005–2012. Intraoperative features and postoperative complications were compared to an age- and sex-matched control group of euthyroid patients operated during the same period. Thyroidectomy was performed by one of the four authors, and each one of them performs approximately 90 to 115 thyroidectomies annually. The primary aim of this study was to assess the differences in operative blood loss, procedure time, and rate of complications of thyroidectomy for euthyroid patients and hyperthyroid patients who did not receive SSI. The secondary aim of this study was to assess the efficacy of β-blockers in preventing cardiac arrhythmia and safety of lithium carbonate in preoperative preparation of refractory HT.

Materials and methods

Case records, operative details, and anesthesia charts of patients who underwent thyroidectomy during 2005–2012 were reviewed. Patients with confirmed diagnosis of HT were included in the study. Diagnosis of HT was made based on clinical features and thyroid function studies (TSH – 0.35–4.9 uIU/ml and free thyroxine [FT4] – 0.7–1.48 ng/dl). Further, all patients underwent^{99} Technetium thyroid scintigraphy, high-resolution ultrasound imaging, and aspiration from the suspicious area. We excluded patients who had recurrent goiter, preexisting vocal cord paralysis, preexisting hypocalcemia, and associated thyroid cancer requiring lymph node dissections. Indications for thyroidectomy included large volume goiter (>90 ml), suspicious nodule, active orbitopathy, recurrence following I^{131} ablation, and patient preference.

An age- and sex-matched control group of euthyroid patients who underwent thyroidectomy during the same period was generated by random pick.

Preoperative preparation

As per the institutional policy, hyperthyroid patients were treated with thionamides (carbimazole or propylthiouracil) and β-blockers (propranolol), but the latter was discontinued when a patient became asymptomatic. We also received patients who were receiving carbimazole and β-blockers from the peripheral centers, and these patients continued to receive β-blockers perioperatively till the 7th postoperative day.

Combination of lithium carbonate, dexamethasone, and β-blockers was used in patients who were refractory to carbimazole (60 mg daily for 1 month) or patients who developed untoward reaction to thionamides. Lithium carbonate sustained release tablet (400 mg) was given three times a day for 6 days along with dexamethasone 4 mg orally three times a day. β-blockers were continued the same dose as before. The patient was operated on the 7th day, and lithium carbonate was discontinued while dexamethasone was continued for 24 h and β-blocker for 7 days.

All patients had complete cardiac assessment with echocardiogram. Preoperative and postoperative assessments of vocal cords were done with video laryngoscope. The euthyroid patients had similar preoperative preparation except for antithyroid medications.

Definitions

Clinical euthyroid state was defined as subjective well-being with heartbeats in normal rhythm and rate (<90/min). Tachycardia during operation was defined as pulse rate above 100/min. The duration of operation was calculated from time induction to complete recovery from anesthesia. The approximate blood loss was calculated based on number of gauze used (5 ml per each piece of 10 cm × 10 cm size). Hypocalcemia is defined as serum corrected calcium level <8.5 mg/dl (8.6–10.2 mg/dl). Permanent hypocalcemia is defined as persistence of low serum corrected calcium after 6 months of operation requiring calcium supplementation. Permanent recurrent laryngeal nerve (RLN) palsy was confirmed when vocal cord movement is absent after 6 months.

Major complications included postoperative bleeding requiring exploration, toxic crisis, permanent hypocalcemia, and permanent RLN palsy. The minor complications included arrhythmia during operation, transient hypocalcemia, transient RLN palsy, surgical site infection, and seroma.

Statistical analysis

The incidences of major and minor complications in group of HT were compared to those of euthyroid group. Further, the procedure time, operative blood loss, and duration of hospital stay were analyzed. The HT group was further subdivided based on preoperative preparations, and group-to-group analysis of all above-noted variables was done. For the comparison of categorical variables among the different groups, Chi-square test was used. For continuous/numerical variables within groups, Mann–Whitney *U*-test was applied because the laboratory parameters values did not follow the parametric assumption. Multivariate analysis was done if the univariate analysis showed significant ($P < 0.05$). SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc was employed for statistical analysis.

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Results

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During the study period, 1881 patients were operated for benign thyroid diseases which included 204 patients with overt HT. We excluded 19 patients with coexisting thyroid cancer with lymph node metastases and 17 with recurrent goiters following less than total thyroidectomy.

We analyzed the data of 168 patients with HT which included 106 patients with GD and 62 with toxic nodular goiter (TNG). Indications for operation included large volume goiter (n = 70), active Grade 2/3 orbitopathy (n = 11), refractory to radioiodine ablation (n = 12), and patient's choice (n = 85). The demography and the American Society of Anesthesiologists physical status of patients in the groups are noted in Table 1.

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Preoperative preparations

Carbimazole was used in 158 patients and propylthiouracil in 6 patients. Propylthiouracil was discontinued in four patients due to lack of compliance and methimazole was started. Ninety-seven patients were getting thionamides alone for a mean period of 24.2 months. Another 71 patients were receiving carbimazole and propranolol for a mean period of 9.75 months (standard deviation = 13.023).

Lithium carbonate was used in combination with dexamethasone and propranolol in six patients. Indications for lithium salts were drug reactions (n = 3) and failure to control toxicity with 60 mg of carbimazole for 2 months (n = 3). The serum FT4 level of 3.934 ng/dl dropped to 1.525 ng/dl on the day of operation and serum TSH 0.0025 uIU/ml changed marginally to 0.015/uIU/ml (all values noted are mean levels). The clinical euthyroid state was achieved in all six patients.

The mean FT4 on the day of operation was 1.119 (0.81–1.79) and TSH was 0.67 uIU/ml (0.01–1.93). Biochemical euthyroid state was not fully achieved in four patients, but the clinical euthyroid state was established in all patients.

The entire cohort underwent total thyroidectomy, and the group-to-group analysis showed extended procedure time and hospital stay in HT group [Table 2]. There was no difference in the operative blood loss.

There was no incidence of toxic crisis. There were 93 (27.6%) minor complications and 5 (1.5%) major complications, and the incidences of minor and major complications were high in HT group [Table 3]. Major complications were only seen in HT group (n = 5; 3%), and this included two incidences of bleeding and three with permanent hypocalcemia. Of the HT group, permanent hypocalcemia occurred only in patients with GD (n = 3; 1.8%, P = 0.010).

There was no difference in intraoperative features and rates of postthyroidectomy complications in patients who received different regimens of preoperative preparation [Table 4].

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Discussion

The overall incidence of major complications in the cohort was 1.5%, which is more than 1% acceptable risk of complications for total thyroidectomy. The major bulk of complications was hypocalcemia (n = 93, 27.6%) and was probably due to setting the cutoff point of serum corrected calcium level at 8.5 mg/dl. Of these, 38 (41%) were asymptomatic and recovered fully after 7 days. However, in general, the complication rates of this series coincide with many other reported series,[12,13,14], and there was no incidence of major complications in euthyroid subgroup.

In general, thyroidectomy for HT carries an excess risk for temporary and permanent hypoparathyroidism.[15,16,17] The present series found significantly higher incidence of symptomatic hypocalcemia in HT group (n = 30, 18% vs. n = 25, 12%) and 18 required intravenous calcium supplementation. The rate of hypocalcemia was not influenced by the type of preoperative preparation.

There were two instances of bleeding requiring exploration, and on both occasions, diagnosis was made immediately after closure of the wound. The sites of bleeding were slipped hemostatic clips from inferior thyroid veins of large volume Toxic Nodular Goiter(TNG) weighing 195 and 263 g. We prefer to relate the bleeding to surgical error and not to a disease-related complication. The single major factor which independently correlated with bleeding during thyroidectomy for GD was weight of the thyroid gland (>200 g).[18] There were thirty patients in HT group with thyroid gland weighing >200 g but showed no significant difference in blood loss (72.62 vs. 69.01 ml).

The probable reason of extended procedure time in HT group was difficulty in mobilization of the gland due to adhesions in perithyroidal soft tissue requiring cautious approach in patients with GD, especially those who received I^{131} ablation. The extended hospital stay in HT group was due to higher incidence of symptomatic hypocalcemia.

Conventionally, iodine preparations were used before thyroidectomy to reduce the operative blood loss. Blood flow estimation with color flow Doppler ultrasonography had shown a significant reduction in thyroid blood flow following iodine usage[19] and thereby reduces operative blood loss.[20] Opinion is still divided since recent systematic review could not find significant advantage in SSI usage.[21] Shinall *et al*. did not find a significant difference in mean estimated blood loss or mean operating time of 162 Graves' patients undergoing total thyroidectomy.[22]

We did not use iodine preparations but did not find excess operative blood loss compared to euthyroid counterparts. Most of the patients in the present series were on thionamides for long duration and were stabilized in euthyroid state. In Graves' patients, euthyroid under treatment, blood flow, and vessel number appeared reduced on color Doppler assessment.[23] We presume that when clinical improvement is established with biochemical euthyroid state, thyroidectomy could be done without excess blood loss. The empirical use of iodine delays adjuvant I^{131} when concurrent thyroid cancer is present.

Several clinical features of thyrotoxicosis are due to increased beta-adrenoceptor upregulation and so β-blockers have become an integral part of management. β-blockers are continued during perioperative period, an attempt to prevent arrhythmia during operation and afterward. Ninety-one patients in the present study were clinically and biochemically euthyroid with thionamides alone. The operative blood loss and procedure time were not different in subgroups of those who received β-blockers and in those who did not. Of the two patients who developed arrhythmia during operation, one was receiving β-blockers. All two had established clinical and biochemical euthyroid state. Intraoperative estimation of serum FT4 and T3 was within normal range, and all these patients had spontaneous recovery. There was no significant difference in the rate of complications in the subgroups receiving thionamides alone or in combination with β-blockers. We presume that routine administration of β-blockers may not prevent arrhythmias during operation and postoperative period and all patients require close monitoring.

Burrow *et al*. demonstrated decreased distribution of radioactive iodine in rats' thyroid follicular cells following short-term administration of lithium.[24] Lithium carbonate inhibits thyroidal iodine uptake and iodotyrosine coupling, alters thyroglobulin structure, and thereby inhibits thyroid hormone secretion.[25] Dexamethasone induces inhibitory effects on thyroid inducing persistent drop in T4 and T3 but preserves the follicular cell response to TSH.[26] Dexamethasone also suppresses the peripheral deionization of T4 to T3.

We used a combination of lithium carbonate and dexamethasone in selected patients of the series and found effective biochemical and clinical control of toxicity. None of the patients experienced drug-related side effects such as transitory gastrointestinal disturbances, mild tremor, or nephrogenic diabetes insipidus. The rate of complications did not differ in six patients who received lithium salts from the other subgroups.

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Conclusion

Total thyroidectomy for HT carries an excess risk for hypocalcemia. Iodine preparations are not mandatory in preoperative preparation since the operative blood loss is similar to euthyroid patients. The routine use of β-blockers may not ensure arrhythmia during operation. Lithium carbonate with dexamethasone is useful preoperative regimen when thionamides are ineffective or contraindicated.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Table 1

Demography and the American Society of Anesthesiologists physical status of patients

Features	HT group (%)	Euthyroid group (%)
Mean age (years)	47.57 (12.900)	45.62 (10.919)
Male sex	39 (23.2)	37 (22)
FT4 value (ng/dl)	2.94 (2.578)	1.167 (0.1727)
TSH (uIU/ml)	0.67 (0.2182)	1.373 (1.260)
ASA PS-1	94 (56)	120 (71.4)
ASA PS-2	49 (29.2)	33 (19.6)
ASA PS-3	14 (8.3)	11 (6.5)
ASA PS-4	9 (5.4)	4 (2.4)
ASA PS-5	2 (1.2)	0

ASA PS: American Society of Anesthesiologists physical status, HT: Hyperthyroidism, TSH: Thyroid-stimulating hormone, FT4: Free thyroxine

Table 2

Details of surgical procedure and hospitalization

Features	HT group	Euthyroid group	*P*
Procedure duration (minutes)	115.75 (29.661)	102.60 (17.648)	0.001
Blood loss (ml)	70.61 (20.296)	70.58 (13.545)	0.985
Weight of specimen (grams)	106.57 (93.184)	103.41 (81.465)	0.741
Intraoperative arrhythmia (%)	3 (1.8)	0	0.082
Postoperative stay (days)	3.91	3.47	0.042

HT: Hyperthyroidism

Table 3

Complications compared to euthyroid patients

Features	HT group (%)	Euthyroid (%)	Total number (%)	P
Postarrhythmia	2 (1.2)	0	3 (0.89)	0.156
Bleeding requiring re-exploration	2 (1.2)	0	2 (0.61)	0.156
Seroma	5 (3)	2 (1.2)	7 (2)	0.252
Temporary hypocalcemia	54 (31)	39 (23.2)	93 (27.6)	0.070
Permanent hypocalcemia	3 (1.8)	0	3 (0.89)	0.082
Temporary RLN palsy	2 (1.2)	2 (1.2)	4 (1.2)	
Permanent RLN palsy	0	0	0	
Overall minor complications	54 (32.1)	39 (23.2)	93 (27.6)	0.013
Overall major complications	5 (3)	0	5 (1.5)	0.024
Total	168	168	336	

RLN: Recurrent laryngeal nerve, HT: Hyperthyroidism

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Table 4

Complication rate of patients in hyperthyroidism group based on preparation

Features	Prepared with thionamide alone (%)	Thionamide with β-blocker (%)	With lithium salts (%)
Arrhythmia	1 (1)	1 (1.4)	0
Procedure time (min)	92.40 (29.631)	92.78 (29.601)	90.00 (30.984)
Blood loss (ml)	70.12 (17.971)	71.06 (23.133)	61.67 (20.167)
Hemorrhage	0	2 (2.8)	0
Hypocalcemia	30 (30.9)	22 (30.6)	2 (33)
RLN palsy*	1 (1)	1 (1.4)	0
Permanent hypocalcemia	1 (1)	1 (1.4)	0
Total	91	71	6

*RLN: Recurrent laryngeal nerve