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Review

Preoperative Preparation in Hyperthyroidism and Surgery in the Hyperthyroid State

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Abstract

Hyperthyroidism is a clinical condition that develops due to the excessive production and secretion of thyroid hormones by the thyroid gland, leading to an elevated concentration of thyroid hormones in tissues. Hyperthyroidism is characterized by low TSH and elevated T3 and/or T4, with the most common causes being Graves' disease, toxic multinodular goiter, and solitary toxic adenoma. T3 is the peripherally active form of thyroid hormone, affecting nearly each tissue and system. The most prominent aspects of hyperthyroidism are related to the cardiovascular system. The treatment of hyperthyroidism includes three options: antithyroid drugs (ATDs), radioactive iodine therapy (RAI), and surgery. Among these treatment modalities, surgery is considered as the most effective one. For patients who are candidates for surgery, preoperative preparation is required to ensure that the thyroidectomy can be performed under optimal conditions. Preoperative preparation should be a combination therapy aimed at preventing the synthesis, secretion, and peripheral effects of thyroid hormones from the thyroid gland. Medications that can be used in this treatment include thionamides, beta-blockers, iodine, corticosteroids, cholestyramine, perchlorate, lithium, and therapeutic plasma exchange. These treatment options can be combined based on the patient's condition. While it is recommended that patients be made euthyroid through preoperative antithyroid treatment to prevent the feared complication, which is the thyroid storm, the supporting evidence is limited. Preoperative treatment does not prevent against thyroid storm whether the patient is euthyroid or hyperthyroid during surgery. Whether surgery should be delayed until biochemical euthyroidism is achieved in hyperthyroid patients remains a topic of debate. Recent studies suggest that thyroidectomy can be safely performed during the hyperthyroid phase by experienced anesthesiologists and surgeons without precipitating thyroid storm or increasing intraoperative and postoperative complications. Although achieving the euthyroid state before surgery is ideal in hyperthyroid patients, it is not always possible. Factors such as allergies to medications, drug side effects, treatment-resistant disease, patient noncompliance, and the urgency of definitive treatment are critical in determining whether hyperthyroidism can be controlled preoperatively. When surgery is necessary in hyperthyroid patients without achieving euthyroidism, the patient's overall condition and comorbidities should be evaluated together by the anesthesiologist, surgeon and endocrinologist, with particular attention to stabilizing the cardiovascular system. We believe that in hyperthyroid patients who are cardiovascularly stable during the hyperthyroid phase, thyroid surgery may not need to be delayed and can be performed safely.

Keywords: Antithyroid drugs, hyperthyroidism, preoperative preparation, thyroidectomy

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Thyroid dysfunction is the second most common endocrine disorder in the general population, following diabetes. The extensity of thyroid dysfunction varies by geographic region, with the prevalences of hypothyroidism ranging from 3.05% to 11.95%, and hyperthyroidism ranging from 0.75% to 2.2%. In all geographic regions, the prevalence of thyroid dysfunction (both hypothyroidism and hyperthyroidism) is higher in women and iodine-deficient areas compared to iodine-sufficient areas.[1-4] TSH concentration increases with age in both men and women. The prevalence of hypothyroidism rises from 18-24 years to over 75 years, reaching 4% and 21% in women, and 3% and 16% in men, respectively.[1]

Patients with thyroid dysfunction may require elective or emergent thyroid and non-thyroid surgery. Thyroid hormones affect almost every system. The general consensus nowadays is that the best outcomes from any type of surgery are obtained when the patient is in the euthyroid state. Regardless of thyroid dysfunction, surgery may sometimes be necessary or performed without achieving euthyroidism. These patients are evaluated preoperatively by an endocrinologist, surgeon, and anesthesiologist, and preoperative treatment is administered.

Sometimes there is no consensus regarding the preoperative treatment and surgical timing for patients with hyperthyroidism. This review aims to assess the preoperative preparation and the potential risks of performing surgery without achieving euthyroidism in these patients, based on current literature.

Hyperthyroidism

Hyperthyroidism is a clinical condition that develops due to the excessive production and secretion of thyroid hormones by the thyroid gland, leading to increased amounts of thyroid hormones in the tissues.[5-7] Hyperthyroidism may be overt or subclinical. Overt hyperthyroidism is defined by reduced thyroid stimulating hormone (TSH) concentrations and elevated levels of triiodothyronine (T3) or free thyroxine (fT4), or both. If serum T3 and fT4 values are within the normal range with reduced TSH levels, it is termed as subclinical hyperthyroidism. The most prevalent causes of hyperthyroidism are Graves' disease, toxic multinodular goiter, and solitary toxic adenoma.[6]

Hyperthyroidism can cause a variety of clinical signs and symptoms, ranging from asymptomatic to thyroid storm, as a result of high thyroid hormone levels. The clinical signs of hyperthyroidism may differ based on the patient's age, gender, duration and cause of the disease, and concomitant conditions.[6] The level of thyroid hormone increase and the severity of clinical findings correlates with each other moderately. While subclinical hyperthyroidism is often assumed to be milder, both overt and subclinical types can lead to distinct signs and symptoms.[6]

Thyroid hormones have impact on nearly all tissue and organ systems. T3 is the active form of thyroid hormone and mediates its cellular effects.[6] The most prominent symptoms related to hyperthyroidism are those involving the cardiovascular system. Thyroid hormone promotes catecholamine signal by increasing the amount of beta-adrenergic receptors on cell surfaces, which improves sympathetic tone.[8] T3 directly has positive inotropic and chronotropic effects on the heart. With their direct impact on the vascular smooth muscles, thyroid hormones reduce systemic vascular resistance and lead to peripheral vasodilation and increased cardiac preload. They also activate the renin-aldosterone system, which results in elevated sodium reabsorption and water retention, leading to a 50-300% increase in cardiac output.[9]

The typical symptoms include palpitations, sweating, shivering, weight loss, anxiety, nervousness, insomnia, fatigue, food cravings, heat intolerance, polydipsia, and hyperdefecation (not diarrhea). Physical findings might consist of tachycardia, tremor, weight loss, muscle weakness, osteoporosis, atrial fibrillation, lid lag, and fixed gaze due to eyelid retraction. The intensity of symptoms and signs may vary depending on the patient and the severity of the disease.[5,7]

The most common clinical manifestations of hyperthyroidism are sinus tachycardia and atrial fibrillation. According to recent research, the incidence of atrial fibrillation in patients with overt hyperthyroidism is between 5% and 15% depending on the study group. Subclinical hyperthyroidism also raises the risk of atrial fibrillation at rates similar to overt hyperthyroidism. Advanced age and male gender are risk factors contributing to the development of atrial fibrillation in hyperthyroidism.[10] Additionally, in the presence of ischemic heart disease, congestive heart failure, or heart valve disease, the risk ratios for atrial fibrillation associated with hyperthyroidism were 1.8, 3.9, and 2.6 times higher, respectively.[11]

Depending on the reason for hyperthyroidism, specific symptoms and signs may appear. Ophthalmopathy, thyroid acropachy and dermopathy can be seen in Graves' disease. In nodular goiter, there may be a sense of globus secondary to tracheal or esophageal compression, dysphagia, or orthopnea.[7] Smoking is an important factor that facilitates the probability of Graves' orbitopathy.[12]

Complications can arise from hyperthyroidism. Elderly patients have a higher risk of developing cardiovascular complications. Although embolic stroke from atrial fibrillation secondary to hyperthyroidism is not rare, the use of anti-

coagulant therapy in those patients is still controversial. Atrial fibrillation in hyperthyroid patients is considered as a risk factor for the development of congestive heart failure. Congestive heart failure in hyperthyroid individuals has been reported as the main cause of cardiovascular events leading to mortality.[7]

Thyrotoxic periodic paralysis is a rare and life-threatening complication of hyperthyroidism that is represented by the triad of muscle weakness, acute hypokalemia, and thyrotoxicosis. If this condition is suspected, treatment with low-dose potassium and non-selective beta-blockers should be started immediately to avoid arrhythmias and improve muscular function.[7]

Osteoporosis and disorders of the reproductive system are the further problems of long-term hyperthyroidism. For instance, men may suffer from gynecomastia, and women may suffer from reduced fertility and menstrual irregularities.[7]

Thyroid storm is a rare, and potentially fatal complication of hyperthyroidism. It presents with high serum thyroid hormone levels and multiple systemic symptoms, indicating an endocrine emergency that requires timely and proper diagnosis and convenient treatment.[13] Thyroid storm should be suspected in patients with thyrotoxicosis who exhibit any signs of systemic decompensation. The most widely accepted diagnostic tool for thyroid storm in thyrotoxic patients is the Burch and Wartofsky scoring system. This system includes parameters such as hyperpyrexia, tachycardia, arrhythmias, congestive heart failure, agitation, delirium, psychosis, stupor, and coma, as well as nausea, vomiting, diarrhea, liver failure, and the presence of a described precipitating factor. The scores in this criteria depend on the seriousness of symptoms, with a total score of >45 indicating thyroid storm, a score of 25-44 suggesting an oncoming thyroid storm, and a score of <25 reducing the possibility of thyroid storm.[14]

Additionally, the Japan Thyroid Association's Thyroid Storm Research Committee conducted an epidemiological study on thyroid storm in 2009 through a survey. According to this study, the incidence of thyroid storm is predicted to be 0.20 per 100,000 people per year, accounting for 0.22% of all thyrotoxic patients and 5.4% of hospitalized thyrotoxic patients, with a mortality rate exceeding 10%.[15] Based on the data from this study, the Japan Thyroid Association and the Japan Endocrine Society published treatment guidelines for thyroid storm. The use of these guidelines is becoming increasingly widespread.[16] In a recent multicentric prospective study in Japan, it was found that while following the guidelines resulted in more severe disease compared to the previous survey, but the prognosis was better (5.5%).[17]

The pathophysiology of thyroid storm is yet unknown, and its clinical manifestations are not directly related to thyroid hormone levels. Hormone levels in thyroid storm resemble those in compensated thyrotoxicosis.[7] A specific precipitating factor is responsible for up to 70% of cases. Irregular usage or withdrawal of antithyroid medications, accompanied by an infection are the frequently seen reasons.[15] Acute illness, thyroid or non-thyroid operations (which have lately become fewer owing to proper preoperative preparation), trauma, stress, and pregnancy are viewed as additional concerns.[7] The treatment approach for thyroid storm is multidisciplinary. The therapy aims to minimize thyroid hormone synthesis, secretion, and circulating thyroid hormone levels, manage the peripheral effects of thyroid hormones, provide symptomatic treatment of systemic signs, and the underlying triggering illness.[7]

Treatment of Hyperthyroidism

There are three treatment options for hyperthyroidism: antithyroid drugs (ATDs), radioactive iodine therapy (RAI), and surgery.[6] The choice of treatment for hyperthyroidism depends on many factors. These include the underlying etiology of hyperthyroidism, the patient's age, symptoms, comorbidities, pregnancy planning, patient's preference, the severity of hyperthyroidism, the probability of remission, access to treatment, and the side effects of the treatment.[5,7] The decision of treatment may also vary depending on the geographic region.[18] Each treatment method has both advantages and disadvantages. These should be discussed with a multidisciplinary team, as well as patients.[19]

Surgery is the most efficient treatment option for all hyperthyroidism etiologies. To ensure that the surgical intervention is performed under optimal conditions, it is necessary to treat thyrotoxicosis during the preoperative preparation of the patients.[20] Preoperative preparation should involve a combination therapy aimed at preventing the synthesis, secretion, and peripheral effects of thyroid hormones from the thyroid gland. Concurrent treatment may also be necessary to reverse any decompensation of normal homeostatic mechanisms.[20] As explained above, elevated thyroid hormones affect many organ systems. However, their most apparent effects are on the cardiovascular system.[6,21]

Antithyroid Treatments

Thionamides

The thionamides used in the treatment of hyperthyroidism are propylthiouracil (PTU), methimazole, and carbimazole, whose active metabolite is methimazole. Thionamides work by blocking thyroid peroxidase, inhibiting iodination, and the coupling of monoiodotyrosine and diiodotyro-

sine, thereby preventing the synthesis of T3 and T4. PTU also inhibits the peripheral deiodination of T4 to T3, which can rapidly reduce T3 levels by up to 50%. Although thionamides prevent new hormone synthesis in the thyroid gland, they do not affect the release of preformed hormones.[20,22] Therefore, euthyroidism can be achieved within 3-8 weeks with thionamides alone.[23]

According to the ATA guidelines for the treatment of hyperthyroidism, methimazole is the first recommended preparation except in cases of the first trimester of pregnancy, thyroid storm, and patients with minor side effects to methimazole.[6] Methimazole has some benefits over PTU: it is more effective, has a longer half-life and duration of action, can be administered once daily when propylthiouracil is used 2-3 times a day, and has fewer side effects.[7] In Graves' disease, according to the ATA guidelines, the starting daily dose of methimazole is approximately 5-10 mg if the fT4 level is 1-1.5 times the upper limit of normal; 10-20 mg if the fT4 level is 1.5-2 times the upper limit; and 30-40 mg if the fT4 level is 2-3 times the upper limit. These recommendations should be individualized based on symptoms, gland size, and total T3 levels.[6] The methimazole dose requirement is generally ≤10 mg per day, in cases of autonomous thyroid nodules.[24] Monitoring serum T3 levels initially is critical because, in some individuals, even if free T4 levels are normalized with methimazole, serum T3 may remain consistently high, stating that thyrotoxicosis is still present.[6] Following the start of treatment, thyroid function tests should be performed every 4-8 weeks. As hyperthyroidism improves, methimazole can be gradually reduced to a maintenance dose of 5-10 mg per day.[24] In severe hyperthyroidism cases where rapid biochemical control is required, an initial dose of 15 or 20 mg administered in two daily doses may be more effective than a single daily dose.

For PTU, treatment typically starts with 50-150 mg three times a day, depending on the severity of hyperthyroidism. Once clinical findings and thyroid function tests return to normal, it is usually possible to reduce the maintenance dose of PTU to 50 mg twice or three times daily.[6]

Sometimes, continuing a higher dose of antithyroid medication along with L-thyroxine treatment, often referred to as block and replace therapy, is not more beneficial than a titration regimen where antithyroid medication is gradually reduced, and it has a higher incidence of side effects.[25] Routine use of this method is not recommended. It is a technique that can be used to quickly achieve euthyroidism in patients with Graves' disease before surgery.[26] In patients who cannot take oral medications, PTU can be administered rectally.[27]

Beta- Blockers

Thionamides prevent the synthesis of new hormones, but since they do not affect the release of preformed hormones from the thyroid gland, it may take several weeks for the patient to achieve a euthyroid state.[20]

Symptomatic treatment is often required for most patients. Beta-blockers should be used in all thyrotoxic patients where there is no contraindication for symptomatic treatment.[28,29] Beta-blockers are a class of drugs that reduce many symptoms associated with thyrotoxicosis, particularly those related to the cardiovascular system. Generally, because the metabolism of beta-blockers is accelerated in thyrotoxicosis, even long-acting agents often require higher doses or more frequent dosing intervals than usual for hypertension treatment. Beta-blockers do not affect thyroid hormone production.

The most commonly used beta-blocker is propranolol. Propranolol has a short half-life and typically requires multiple doses per day. Therefore, any missed or delayed doses can lead to a return of thyrotoxic parameters, as noted in reports of preoperative preparation with a single dose of propranolol. The effective daily dose of propranolol ranges from 40-320 mg.[20] High doses of propranolol (40 mg four times daily) inhibit the peripheral conversion of T4 to T3. This effect is not observed with other agents.[29]

Long-acting atenolol doses can range from at least 50 mg to more than 200 mg per day and should be administered twice daily for decent control over a 24-hour period. For hospitalized patients who cannot be treated with oral beta-blockers or have severe thyrotoxicosis, an intravenous preparation can be given. In patients requiring a faster effect (e.g., poorly controlled atrial fibrillation), intravenous loading with metoprolol or esmolol has been effectively used.[20]

Beta-blockers are not recommended for patients with bronchospastic asthma. In such circumstances, beta-1 selective medicines (atenolol or metoprolol), ACE inhibitors, or calcium channel blockers (diltiazem, verapamil) can be administered.[28,29] Cardioselective beta-blockers have a higher cardioprotective effect and are superior in preventing atrial fibrillation. In thyrotoxic patients, if digoxin is used, higher doses are generally required.[29]

In patients where beta-blockers are contraindicated, drugs like reserpine and guanethidine, which reduce sympathetic nervous system activity by inhibiting the storage and release of norepinephrine in vesicles, can be used. Reserpine can be administered intramuscularly at a dose of 2.5-5 mg every 4 hours, and guanethidine can be taken orally at a dose of 30-40 mg every 6 hours.[20]

Iodine

In the preoperative preparation of thyrotoxic patients, iodine shows its effects most rapidly. At supraphysiological doses, iodine reduces the synthesis of new hormones by inhibiting its own organification (known as the Wolff-Chaikoff effect) and acutely lowers peripheral thyroid hormone concentrations by reducing secretion. The Wolff-Chaikoff effect begins within 24 hours of iodine intake and reaches its maximum effect around day 10 of treatment.[6,20] After day 10, escape from the Wolff-Chaikoff effect begins, and iodine starts to be used in thyroid hormone production (known as the Jod-Basedow effect). Additionally, in cases with toxic thyroid nodules, iodine again has the potential to increase thyroid hormone production through the Jod-Basedow effect. However, in Graves' disease, the Jod-Basedow effect does not apply immediately after iodine administration.[21] Due to the potential hyperthyroid effects of iodine, preoperative iodine administration is generally not recommended in patients with toxic nodules.[6]

If preoperative iodine is to be administered, thionamides should be started before iodine treatment in both patients with toxic nodules and those with Graves' disease. But, in Graves' patients who cannot tolerate thionamides, treatment with just iodine and β-blockers may still be effective. Due to the escape from the Wolff-Chaikoff effect, iodine treatment should not be continued for more than 10 days before surgery.[21]

In addition to these effects, preoperatively administered Lugol's solution in patients with Graves' disease has been shown to reduce thyroid blood flow, thyroid vascularity, systemic angiogenic factors such as vascular endothelial growth factor (VEGF), and intraoperative blood flow.[30,31] Huang et al.[30] recommend preoperative iodine administration in all Graves' disease patients because these effects of iodine are observed even in euthyroid patients.

In hyperthyroid patients, it is calculated that a daily dose of up to 6 mg of iodine is sufficient to reduce thyrotoxicosis, and increasing the dose does not reinforce the effect of iodine. In spite of that, the preoperative dose of iodine is generally higher than this amount.[20] Iodine is commonly administered orally but can also be given rectally or intravenously. Iodine is provided as potassium iodide, with Lugol's solution (5-7 drops, 0.25-0.35 ml) or saturated solution of potassium iodide (SSKI) (1-2 drops, 0.05-0.1 ml) three times a day being mixed with water or fruit juice for oral administration. Each drop of Lugol's solution contains 8 mg of iodine, and each drop of SSKI contains 50 mg of iodine.[32] These preparations can also be diluted with water and administered via rectal enema if necessary.[27]

Oral Iodine-based Radiographic Agents

Oral iodine-based radiographic contrast agents, such as iopanoic acid (IOP) or ipodate, can provide much faster control of thyrotoxicosis. These agents are typically used in conjunction with other antithyroid medications. They have numerous effects on thyroid physiology and thyroid hormone metabolism. They inhibit the deiodination of T4 to T3 in the thyroid and reduce thyroid hormone secretion. Additionally, they decrease the peripheral conversion of T4 to T3, leading to a rapid reduction in T3 levels. The iodine released from these agents also reduces iodine organification in the thyroid and decreases thyroid hormone secretion, which lowers T4 levels. Nonetheless, the effect on serum T4 levels is slower compared to potassium iodide treatment. Since prolonged use of these agents can exacerbate hyperthyroidism, they should be used only for short periods. Ipodate, for example, was used in the past but was withdrawn from the market in the U.S. approximately 20 years ago.[33,34] Currently, IOP preparations are available. For preoperative preparation, IOP-containing agents can be administered at a dose of 500 mg once to four times daily.[34,35] In emergencies, sodium iodide can be used intravenously at a dose of 0.5-1 g every 8 hours.[9,21,32,36]

Corticosteroids

Corticosteroids have several impacts on thyroid function. High doses of glucocorticoids reduce the peripheral conversion of T4 to T3. Additionally, in Graves' disease, they decrease serum T4 concentrations either by directly affecting the thyroid or by reducing the production of thyroid-stimulating immunoglobulins, which in turn reduces T4 secretion.[37] In thyrotoxic patients, adrenal reserve may be inadequate, therefore corticosteroids remove the risk of adrenal insufficiency associated with thyrotoxicosis.[23] For low adrenal reserve, stress-dose glucocorticoids should be administered. This dosage also inhibits the conversion of T4 to T3.[38]

The effect of steroids on thyroid hormone conversion begins within a few hours. Recommendations are as follows: 100 mg of hydrocortisone orally or IV every 8 hours, 2 mg of dexamethasone orally or IV every 6 hours, or 0.5 mg of betamethasone orally, intramuscularly, or IV every 6 hours.[21] These doses should be administered intravenously on the day of surgery and then gradually decreased over the next three days postoperatively.[38]

Cholestyramine

Cholestyramine, also known as bile acid sequestrant, isan ion exchange resin. It inhibits the enterohepatic circulation of thyroid hormones and can be used to manage hyperthyroidism. Both T3 and T4 reach the enterohepatic

circulation, predominantly in conjugated form, but also in trace amounts as unconjugated hormones. An in vitro study found that 50 mg of cholestyramine resin could bind at least 3000 µg of thyroxine. Additionally, even a small amount of cholestyramine may notably hinder the transport of thyroxine across the intestinal wall in rats. Given that the enterohepatic circulation of thyroid hormones is increased in thyrotoxicosis, cholestyramine is quite effective, contributing to the rapid reduction of thyroid hormone levels.[21,39] In Graves' disease, it has been shown that a combination of cholestyramine and thionamides achieves euthyroidism more quickly than thionamides alone. It is typically administered at a dose of 4 grams, 2 to 4 times a day.[39] In the meantime, it has also been shown that a lower dose of 1-2 grams of cholestyramine taken twice daily can be effective.[40]

Perchlorates

Perchlorates are ionic inhibitors that block thyroid hormone synthesis by preventing the transport of iodine into thyrocytes. They achieve this by competitively interfering with the Sodium-Iodine Symporter at the basolateral membrane of thyrocytes.[41] Furthermore, perchlorates have the ability to deplete iodine from the thyroid gland. When applied orally, potassium perchlorate can quickly discharge stored intrathyroidal iodide in patients with Graves' disease using thionamides.[39]

Perchlorate has a short half-life when taken orally, with its therapeutic effect lasting over 8 hours following a single dose. To maintain consistent pharmacological effects over a 24-hour period, it should be administered 3-4 times a day. Perchlorate concentrations peak in plasma within a few minutes after administration and reach their maximum in the thyroid approximately 4 hours later. The pharmacological effect of perchlorates depends on the circulating perchlorate-iodine ratio, the severity of hyperthyroidism, and the antithyroid treatments being administered, such as thionamides.[41]

Potassium perchlorate comes in 200 mg hard gel capsules. The initial dose is 200 mg (1 tablet) three times a day (600 mg total). The effective total daily dose of potassium perchlorate should be at most 1,000 mg. Oral drops containing sodium perchlorate (344 mg per mL of solution) are available. The effective daily dose ranges from 800 to 1,000 mg, which are commonly provided as 10 drops four to five times each day.[41]

Although perchlorates are not typically taken into account as a first-line treatment for hyperthyroidism, they can be used in serious situations such as thyroid storm, in preparation for thyroid surgery, in amiodarone-induced thyrotoxicosis, or as part of combination therapy to avoid high doses of thionamides due to their rapid onset of action. They may also be considered an alternative treatment when thionamides are contraindicated or not tolerated.[41]

Lithium

Lithium has an elimination half-life of approximately 18-36 hours and is primarily excreted through the kidneys. In cases of renal impairment and increasing age, it is believed that lithium clearance declines.[39,42]

Lithium is thought to accumulate in the thyroid gland at concentrations 3 to 4 times higher than in plasma. The primary mechanism of lithium is the inhibition of thyroid hormone release by blocking the effect of TSH on cAMP. Lithium may also inhibit thyroid hormone synthesis. In patients with hyperthyroidism, serum thyroxine levels often drop to about 25-32% of baseline levels after one week of lithium treatment. Although data is limited, it has been suggested that the thyroid gland may escape the inhibitory effects of lithium.[39,42]

Due to its side effects and narrow therapeutic range, lithium is not considered a first-line treatment for hyperthyroidism. Additionally, experience with its use in thyrotoxicosis is limited. However, lithium can be used for temporary control of hyperthyroidism in patients who cannot use thionamide medications, as an alternative treatment for thyroid storm, and for rapid preparation for thyroidectomy. Furthermore, lithium has been suggested as an adjunct to RAI therapy for hyperthyroidism, as it inhibits iodine release from the thyroid gland without affecting the uptake of RAI, thereby increasing RAI retention.[39,42]

Lithium dosing typically involves taking 300-450 mg orally every 8 hours. Elderly patients, due to decreased total body water and glomerular filtration rate, require a lower dose to maintain therapeutic levels. For patients over 60 years of age, the daily dose should be between 500 and 750 mg, and for those over 80, it should not exceed 450 mg daily.

Monitoring of Lithium Levels: Serum lithium levels should be monitored weekly after starting treatment and following dose adjustments until the achievement of therapeutic levels. The serum lithium concentration should be maintained within the range of 1 mEq/L. Blood samples for testing should be taken 12 hours after the last dose.[39]

Studies have shown that optimal lithium blood levels for controlling thyrotoxicosis range from 0.6 to 1.2 mmol/L. In order to prevent toxic levels, it is preferable to keep serum lithium levels below 1.0 mmol/L, ideally around 0.5 mmol/L.[43]

Therapeutic Plasma Exchange

In the latest version of the Therapeutic Apheresis guidelines updated in 2019 by the American Society for Apheresis, therapeutic plasma exchange is recommended as a category II indication for the treatment of thyroid storm. It can be used alone or in combination with other treatments as a second-line therapy. However, the evidence in the literature on this topic is of low quality, and the recommendation level is grade 2C.[44]

In addition, this guideline does not provide recommendations for the use of therapeutic plasma exchange (TPE) specifically in the context of thyrotoxicosis. Recently, there is growing evidence that TPE can be successfully used to reduce thyroid hormones in cases of severe hyperthyroidism that cannot be controlled with other treatments, in patients with contraindications to other therapies, or as preoperative preparation in severe hyperthyroidism. These studies indicate that multiple sessions of TPE may be required to stabilize the patient. TPE can be used in conjunction with other antithyroid treatments.[45-47] TPE rapidly lowers thyroid hormone levels and also reduces autoantibodies, binding proteins, cytokines, and catecholamines in Graves' disease.[44]

Preoperative Rapid Preparation in Hyperthyroidism

In patients scheduled for surgery, achieving preoperative euthyroidism with thionamides requires a specific period. In cases where thionamides are contraindicated or there is insufficient time to achieve euthyroidism with thionamides alone, quicker preparation for surgery may be necessary. Various treatment strategies have been suggested for rapid preoperative preparation. These strategies typically involve different combinations of the mentioned medications.[26,38]

In hyperthyroid patients, euthyroidism can be achieved within an average of 7 days using a combination of IOP (500 mg twice daily), dexamethasone (1 mg twice daily), a beta blocker, and, if possible, a thionamide.[33]

In another study, for patients who could not achieve euthyroidism with antithyroid drugs or who had additional conditions such as pregnancy or hypertension, a rapid preparation regimen using oral betamethasone (0.5 mg every 6 hours), IOP (500 mg every 6 hours), and propranolol (40 mg every 8 hours) was administered. Although serum T4 levels significantly decreased over 5 days, they did not reach euthyroid levels. In contrast, serum T3 levels decreased to euthyroid values, and clinical euthyroidism was achieved, allowing for a safe thyroidectomy without local or systemic complications.[48]

In another study, for patients who experienced serious side effects from thionamides or had treatment non-compliance, a combination of 5% Lugol's solution (13 drops three times a day, approximately 81.25 mg of iodine), dexamethasone (2 mg twice daily), and beta blockers (propranolol, metoprolol, or bisoprolol) adjusted to achieve a heart rate of <80 beats/minute provided rapid and effective preoperative preparation within 10 days.[49]

Data from patients prepared for surgery with classic treatments were retrospectively compared with those prepared quickly using different drug combinations. According to this study, rapid preoperative preparation was found to be effective and safe, with similar postoperative complication rates compared to classic treatment, and it was reported as a time-saving method.[50]

Another study reported that in patients where euthyroidism could not be achieved with thionamides or those with drug reactions, a combination of lithium carbonate and dexamethasone was effective for preoperative preparation. The study also found that postoperative complication rates were similar to those seen with other methods.[51]

Most studies on rapid preoperative preparation are retrospective and lack control groups. However, based on the available data, it can be said that rapid preoperative preparation is effective and safe and can be applied when necessary.

Is Preoperative Euthyroidism Mandatory?

The American Thyroid Association and the American Association of Endocrine Surgeons propose that, if surgery is the desired treatment for hyperthyroidism, patients should become euthyroid preoperatively with antithyroid treatment to avoid the feared complication of thyroid storm. Although this is defined as a strong recommendation, it is noteworthy that the level of evidence remains low quality.[6,19] Nonetheless, the American Association of Endocrine Surgeons guidelines state that even in patients who have been rendered euthyroid preoperatively, thyroid surgery still carries a potential risk for thyroid storm.[19]

In recent years, the risk of perioperative thyroid storm in hyperthyroid patients undergoing surgery under different preoperative treatment strategies has been addressed in a systematic review. The study evaluated 26 retrospective or prospective cohort studies and 31 case reports or case series. All 26 studies had varying levels of critical bias. There were no studies comparing the risk of thyroid storm between hyperthyroid patients without preoperative preparation and those who received preoperative treatment to achieve clinical euthyroidism. In the literature, preoperatively unprepared cases of perioperative thyroid storm are

reported as case reports, with many of these cases involving patients who were undergoing non-thyroid emergent surgery without prior knowledge of their hyperthyroid state, or sometimes elective non-thyroid surgery. The study underlined the lack of definitive evidence on the risk of perioperative thyroid storm in patients with and without preoperative preparation. However, given the severity of this complication and the difficulty in identifying patients at increased risk, the authors recommended adherence to current relevant guidelines for preoperative treatment of patients undergoing elective surgery. Nonetheless, the authors noted that in the studies included in this review, thyroid storm occurred independently of preoperative treatment and, interestingly, in both euthyroid and hyperthyroid patients.[52]

It is convenient to state that there is consensus in guidelines and classic textbooks regarding the recommendation of preoperative antithyroid treatment and/or other therapeutic options for preparing hyperthyroid patients for surgery. In contrast, none of these guidelines or textbooks reference studies providing evidence that preoperative treatment for hyperthyroidism reduces the incidence of thyroid storm. Thyroid storm can still occur regardless of the choice of preoperative treatment method. Therefore, preoperative treatment does not protect a euthyroid or hyperthyroid patient from thyroid storm.[52] Whether surgery should be delayed until biochemical euthyroidism is achieved in hyperthyroid patients remains a topic of debate.

In three cohort studies (two retrospective and one prospective) involving a total of 290 patients who were prepared for surgery with only beta-blockers, all patients were biochemically hyperthyroid during surgery, and none developed thyroid storm.[53-55]

In a prospective randomized study comparing methimazole with selective beta-1 blocker metoprolol in 30 patients, 15 patients in the metoprolol group were biochemically hyperthyroid. Both groups had similar gland vascularity, technical difficulty, blood loss, and operation time. There were no anesthesiologic or cardiovascular complications in either group.[56]

Between 1959 and 1970, among 272 patients who received preoperative thionamide treatment, 17 were switched to iodine therapy due to side effects, and 7 patients did not receive any treatment. Among these patients, one developed thyroid storm; it was noted that this patient had incomplete preoperative preparation with iodine, but it was not specified whether the patient was euthyroid or hyperthyroid during the surgery.[57]

Five recent studies involving 1,287 cases of patients prepared for surgery with thionamides, iodine, beta-blockers, and steroids, either alone or in various combinations, show case numbers ranging from 67 to 594. In these studies, the incidence of hyperthyroid cases during surgery ranges from 21% to 52.3%. With the exception of one case, thyroid storm was not reported in any of the euthyroid or hyperthyroid cases.[58-62]

Yamanouchi et al.[61] divided patients into three groups based on their fT3 levels: well-controlled group (fT3 ≤6.0 pg/mL), moderately controlled group (fT3 >6.0, ≤10.0 pg/mL), and poorly controlled group (fT3 >10.0 pg/mL). The study reported that in the moderately controlled group, one patient showed symptoms suspected to be thyroid storm, but these symptoms spontaneously decreased without leaving any sequelae. In the poorly controlled group, the proportion of patients receiving preoperative beta-blockers was significantly higher than in the other two groups ($p<0.01$, $p<0.05$ each). One hour after the onset of general anesthesia, in the poorly controlled group, the heart rate was significantly higher than in the well-controlled group ($p<0.05$). During the surgery, the proportion of patients receiving beta-blockers in the poorly controlled group was significantly higher compared to both the well-controlled and moderately controlled groups ($p<0.001$, each). Apart from this, there was no significant difference between the groups in terms of surgical duration, amount of bleeding, or postoperative temporary and permanent complications.

Cipallo et al.[59] did not identify hyperthyroidism during surgery as a significant risk factor for the development of complications in their bivariate analysis.

Shinall et al.[60] did not find a correlation between thyroid hormone status and complications in both bivariate and multivariate analyses. In 70 hyperthyroid patients (42%) (mildly, moderately, or severely), the rate of intraoperative beta-blocker administration was not significantly different from that in euthyroid and hypothyroid patients. However, the use of beta-blockers was higher in patients with moderate and severe hyperthyroidism compared to all other patient groups (odds ratio 2.65, 95% CI 1.16-6.01).

In the study by Fazedin et al.,[62] patients were divided into two groups based on preoperative T3 and T4 levels: controlled and uncontrolled. Although preoperative thyroid storm was higher in the uncontrolled group (6.4% vs. 1.5%; $p=0.008$), no thyroid storm precipitated by surgery was detected in either group. The controlled group had shorter surgery times and lower estimated blood loss. Despite a higher rate of transient hypocalcemia in the uncontrolled group (13.4% vs. 4.7%; $p=0.013$), the rates of other transient and permanent complications were similar between the groups. They suggested that the higher incidence of transient hypocalcemia might be due to more severe hungry

bone syndrome in the uncontrolled group. They proposed that thyroidectomy can be safely performed in actively hyperthyroid patients without necessarily being limited to an euthyroid phase.

In a study comparing data from 12 controlled and 17 uncontrolled (with preoperative FT4 >1.7 ng/dL and TSH <0.3 µIU/mL) Graves' disease patients, no cases of thyroid storm occurred in either group. Between the groups, there were no differences in intraoperative vital signs or anesthetic agents used. In particular, among extremely uncontrolled patients (preoperative FT4 >3.4 ng/dL and TSH <0.3 µIU/mL), the proportion of patients using preoperative beta-blockers, the duration of surgery, and the amount of intraoperatively used remifentanil were significantly higher. In the uncontrolled Graves' disease group, there were no changes in vital signs observed during surgery despite fT4 levels reaching up to twice the normal upper limit. Postoperatively, all patients had stable vital signs within normal limits.[63]

Akram et al.[64] evaluated the impact of applying ATA guideline criteria for preoperative preparation of Graves' disease patients on surgical outcomes. The researchers assessed intraoperative hemodynamic stability (blood pressure, heart rate) and postoperative surgical complications. They also compared data between euthyroid and hyperthyroid patients. No cases of thyroid storm were detected in either group. Of the patients, 165 (72%) were euthyroid (T4 levels <1.5 ng/dL), and 63 (28%) were hyperthyroid. The highest preoperative T4 value was 8.5 ng/dL, with 95% of patients having levels below 3 ng/dL. The rate of normal heart rate during surgery (defined as a starting heart rate <90 beats per minute (bpm) in the operating room) was higher in euthyroid patients compared to non-euthyroid patients (75% vs. 62%; p=0.05). There was no serious difference in blood pressure control between euthyroid and hyperthyroid patients. The rate of intraoperative beta-blocker use was higher in the hyperthyroid group (23.5% vs. 11.6%; p=0.04). In spite of the different strategies used in heart rate control during surgery, hospital stay duration and any postoperative complications were not associated with the euthyroid status. The researchers concluded that preoperative methimazole administration for symptomatic treatment remains convincing, but full control may not be necessary to ensure intraoperative safety and optimize postoperative outcomes.

Additionally, the researchers concluded that adherence to ATA guidelines for preoperative preparation of hyperthyroid patients is not a must for outstanding postoperative results. While guideline-compliant preoperative preparation reduced the incidence of intraoperative tachycardia, it did not affect intraoperative hypertension, surgery duration, or postoperative complications. Based on these results, they suggested that adherence to ATA guidelines may not be necessary to optimize surgical outcomes, particularly in high-volume and experienced centers.[64]

In another retrospective study, 151 patients who underwent thyroidectomy for hyperthyroidism were analyzed, including 57 with perioperative hyperthyroidism and 94 euthyroid patients. The study assessed 30-day mortality, length of hospital stay post-surgery, intraoperative findings related to thyrotoxicosis (e.g., heart rate >100 bpm, systolic blood pressure >180 mmHg or <60 mmHg, or temperature >38°C), intraoperative beta-blocker use, and the level of care required postoperatively. No 30-day mortality was detected. There were no significant differences between the two groups regarding intraoperative thyrotoxicosis findings or postoperative care. A greater rate of intraoperative beta-blocker use in the hyperthyroid group (28.1% vs. 8.5%, p=0.002) was the only important change. The researchers reported that thyroidectomy performed by an experienced thyroid surgeon and anesthesiologist in cases of mild to moderate biochemical hyperthyroidism may not be associated with an increase in adverse intraoperative and postoperative outcomes.[65]

In a retrospective study evaluating data from 248 patients who started preoperative thionamide therapy, 17 patients discontinued thionamides and were treated with various combinations of beta-blockers, Lugol's iodine, steroids, and cholestyramine before surgery. In the group where thionamides were not administered, preoperative fT4 levels were higher compared to the group that received thionamides (1.5 vs. 1.1 ng/dL, p<0.01), and the rate of intraoperative beta-blocker use was higher (65% vs. 40%, p=0.01). The researchers reported that thyroidectomy could be performed without enhancing intraoperative and postoperative complication rates or the risk of thyroid storm in patients who could not tolerate thionamides.[66]

The review highlighted that thyroid storm is most commonly reported in thyroidectomy series from studies conducted in the 1980s and earlier. More recent studies on thyroid storm are primarily case series or case reports. Effective preoperative treatment, advancements in anesthesia drugs, and improvements in intraoperative monitoring have contributed to making thyroidectomy a rare triggering factor for thyroid storm.[67] A cohort study evaluates the surgical outcomes of patients who are operated on after developing thyroid storm. The study consisted of 17,175 patients diagnosed with thyroid storm from the 2016-2020 National Inpatient Sample in the United States. It was observed that the need for thyroidectomy at the time of presentation with thyroid storm is rare, occurring in approximately 4% of

patients. Multivariate analysis identified predictive factors for the need for thyroidectomy in those patients, as Graves' disease (adjusted odds ratio [AOR] 3.16, 95% Confidence Interval [CI] 1.99-4.98, p<0.001), toxic nodules (AOR 4.60, 95% CI 1.59-13.3, p=0.005), acute decompensated heart failure (AOR 1.62, 95% CI 1.02-2.58, p=0.039), and acute renal failure (AOR 2.02, 95% CI 1.15-3.55, p=0.014). The overall complication rate, including postoperative hematoma, vocal cord paralysis, and hypocalcemia, was 30%. No surgical effect on mortality was detected.[67]

A study evaluated the surgical outcomes of 30 patients who were admitted with a diagnosis of thyrotoxicosis and underwent emergency thyroidectomy during the same hospital admission. Of these patients, 26.7% were diagnosed with thyroid storm. Comorbid conditions included atrial fibrillation (53.3%), heart failure (40%), and liver failure (16.7%). The indications for surgery included adverse drug reactions (30%), inadequate therapeutic effect (30%), and worsening heart failure (26.7%). Postoperatively, 6.7% of patients required reoperation for neck hematoma, 13.3% developed transient hypoparathyroidism, and 6.7% experienced hoarseness. Of the patients with atrial fibrillation, 50% improved, and 50% of those suffering from heart failure with reduced ejection fraction showed ultrasonic improvement. One patient (3.3%) died from liver failure. The researchers noted that patients needing emergent thyroidectomy often have life-threatening comorbidities, particularly cardiovascular diseases. They suggested that performing thyroidectomy in these patients might potentially create clinical homeostasis for the management of comorbid conditions.[68]

Even though reaching euthyroid status before surgery is ideal for hyperthyroid patients, it is not always possible. Factors such as allergic reactions to drugs, adverse effects of medications, resistance to treatment, patient non-compliance, and the urgency of definitive treatment are significant in determining whether hyperthyroidism can be managed before surgery. The accessibility of treatment options for the patient population and patients' sociocultural levels can also influence the ability to achieve euthyroid status. Additionally, family physicians and endocrinologists may be hesitant to refer patients for surgery without reaching euthyroidism.[62] Even when clinical euthyroidism is achieved before surgery in planned surgical patients, elevated biochemical T3 and/or T4 levels above reference values may lead anesthesiologists or endocrinologists to postpone the surgery. It has been argued that delaying the operation to achieve euthyroid status in these patients may lead to persistent symptomatology, chronic medical treatment, and even inpatient care, causing stress and increasing costs.[62] Many studies mentioned above have shown that in experienced centers, thyroidectomy can be performed without precipitating thyroid storm and without increasing intraoperative and postoperative complication rates in hyperthyroid patients. It is critical to perform surgery in centers with experienced surgeons and anesthesiologists for hyperthyroid patients. Regardless of the level of preoperative control of hyperthyroidism, careful perioperative management of these patients is crucial to achieving optimal outcomes. Particularly, ensuring cardiovascular stabilization, preventing decompensation, and monitoring the patient are essential.[58] Early surgery has also been presented to enhance biochemical recovery in hyperthyroid patients.[58,60,69]

When surgery is required in hyperthyroid patients without achieving euthyroidism, the anesthesiologist, surgeon, and endocrinologist should together evaluate the patient's overall condition and comorbidities, with particular attention given to stabilizing the cardiovascular system. We believe that thyroid surgery in the hyperthyroid phase can be safely performed without a delay in patients with cardiovascular stability. Based on the timing of the surgery, combined treatment mechanisms should be initiated according to thyroid hormone synthesis, secretion, and peripheral effects. A specific treatment and precaution plan should be structured depending on the patient's comorbidities.

Additionally, non-thyroid emergency surgical interventions may be necessary in hyperthyroid patients. As soon as surgery is planned and thyroid dysfunction is detected, preparations should immediately begin to ensure cardiovascular and hemodynamic stability and prevent decompensation. An optimized combined treatment plan should be implemented targeting thyroid hormone synthesis and secretion (thionamides, iodine), peripheral sympathetic effects of thyroxine (beta-blockers, corticosteroids), and systemic decompensation (fluids, nutrition).[70]

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