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Research Article

Rapid Preoperative Optimization of the Thyrotoxic Patient Awaiting Oncological Surgery: a Lithium-Based Multimodal Protocol Using Immediate-Release and Slow-Release Formulations

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ABSTRACT
Patients referred for thyroidectomy or other urgent surgery in the setting of active thyrotoxicosis present a recurring clinical dilemma, particularly in endocrine and oncological practice. Standard guidance is to render the patient euthyroid before operation to avoid precipitating thyroid storm, but the conventional thionamide-based pathway requires several weeks. In patients with aggressive or rapidly progressive thyroid malignancy, or with non-thyroidal cancer requiring surgery in a thyrotoxic state, this delay can allow tumour progression to the point of inoperability. There is therefore a genuine need for a structured, rapid optimization strategy that achieves operative safety within days rather than weeks. This review summarizes the rationale and evidence for a multimodal rapid-preparation protocol built around lithium carbonate, an inhibitor of thyroid hormone release that acts independently of the thionamide pathway and is therefore useful when thionamides are contraindicated, not tolerated, or too slow. Two operational variants are presented: one using immediate-release lithium, and one using slow-release lithium for settings where immediate-release preparations are unavailable. Each is combined with beta-adrenergic blockade, glucocorticoids, inorganic iodine, and bile-acid sequestrants, with therapeutic plasma exchange reserved as rescue. Dosing, serum-level targets, monitoring, drug-interaction caveats, and the limitations of the underlying evidence are discussed. The aggregate evidence is dominated by case series, small cohorts, and systematic reviews of these, rather than randomized trials; the protocol should be applied selectively, under close biochemical and renal monitoring, and with multidisciplinary input.

Keywords: Thyrotoxicosis, Lithium Carbonate, Preoperative Preparation, Thyroidectomy, Thyroid Storm, Therapeutic Plasma Exchange, Thyroid Cancer.

INTRODUCTION

Thyrotoxicosis encompasses multiple aetiologies and a spectrum of severity, and its appropriate management depends on accurate diagnosis and on coexisting conditions [1]. When surgery is required in a thyrotoxic patient, current guidelines recommend achieving a euthyroid or near-euthyroid state preoperatively, because anaesthesia, surgical stress, and gland manipulation can precipitate thyroid storm, a decompensated state carrying a mortality of roughly 10 percent or higher even with modern care [1,5,6]. The standard route to that goal is a thionamide (methimazole, carbimazole, or propylthiouracil), which inhibits new hormone synthesis but does not lower the large pool of preformed, stored hormone; biochemical control therefore typically requires several weeks [1,3].

This timeline is problematic in a specific and clinically important scenario. Patients are referred from endocrine and surgical oncology services for preoperative optimization of thyrotoxicosis arising either from a thyroid malignancy itself or from coincident hyperthyroidism in a patient who requires cancer surgery. In a proportion of these patients, the weeks spent rendering them biochemically fit are weeks during which an aggressive tumour can progress, regional or distant spread can occur, and a resectable lesion can become inoperable. The window for curative surgery and the window for safe anaesthesia are in direct tension. A rapid, reproducible optimization strategy that

compresses preparation from weeks into days is therefore of real value, provided it can be delivered safely.

The 2016 American Thyroid Association guidelines acknowledge second-line and adjunctive agents for patients who cannot follow the standard path, but provide limited prescriptive detail for the patient who is thionamide-intolerant or for whom thionamide therapy alone is inadequate or too slow [1,2]. A recent systematic review of perioperative thyrotoxicosis specifically addressed this gap, concluding that adjunctive pharmacotherapy with or without therapeutic plasma exchange allowed patients to proceed to surgery without perioperative thyroid storm and achieved substantial reductions in circulating free thyroxine (FT4) and free triiodothyronine (FT3) [2]. Against that background, this review consolidates the mechanistic rationale and the available evidence for a lithium-anchored multimodal protocol and presents two practical operational variants for rapid preoperative use.

The Clinical Problem and Therapeutic Rationale

Thyroid hormone exerts genomic and non-genomic effects across virtually every organ system, with the cardiovascular consequences, sinus tachycardia, atrial fibrillation, high-output strain being the most immediately dangerous in the perioperative period [1,5]. The Burch–Wartofsky Point Scale remains a widely used bedside instrument for estimating the likelihood that a thyrotoxic patient is progressing toward storm, and the Japan Thyroid Association criteria provide a complementary diagnostic framework; both reinforce that severe thyrotoxicosis is a continuum rather than a binary state [5,6]. The therapeutic objective of rapid preparation is therefore twofold: to blunt the peripheral action of circulating hormone immediately, and to lower the circulating hormone concentration itself as quickly as is safely possible.

Achieving this rapidly requires attacking several points in hormone economy simultaneously: synthesis (thionamides, where usable), peripheral T4-to-T3 conversion (beta-blockade, glucocorticoids), release of stored hormone (lithium and, after thionamide loading, inorganic iodine), enterohepatic recirculation (bile-acid sequestrants), and, as a rescue measure, bulk extracorporeal removal (therapeutic plasma exchange) [2,3]. Lithium occupies a particular niche in this scheme because it inhibits hormone release through a mechanism entirely independent of the thionamide pathway, making it valuable precisely when thionamides have failed or cannot be used.

Pharmacological Components of Rapid Preparation

Beta-Adrenergic Blockade

Beta-blockade is the cornerstone of symptomatic control and is recommended in essentially all symptomatic thyrotoxic patients without contraindication [1]. Propranolol is commonly preferred because, in addition to controlling heart rate and adrenergic symptoms, at higher doses it modestly inhibits peripheral conversion of T4 to the more active T3. A typical oral regimen is propranolol 40–80 mg every 6–8 hours, titrated to a resting heart rate below approximately 90 beats per minute; a cardioselective agent (for example, atenolol) is substituted when bronchospastic disease makes a non-selective agent unwise [1,3]. Beta-blockade treats the haemodynamic phenotype but does not lower hormone levels, and is therefore necessary but not sufficient.

Glucocorticoids

Glucocorticoids reduce peripheral T4-to-T3 conversion and address the relative adrenal insufficiency that can accompany severe thyrotoxicosis. Acute administration of corticosteroids was shown decades ago to lower thyroidal activity and circulating T3 in Graves' disease, and they remain a standard component of storm and pre-storm management [9,6]. Practical regimens are dexamethasone 2 mg every 6–8 hours or hydrocortisone 100 mg every 8 hours; dexamethasone has the advantage of a well-characterized inhibitory effect on conversion [9].

Bile-Acid Sequestrants (Cholestyramine)

Thyroid hormones undergo enterohepatic recirculation, which is increased in thyrotoxicosis. Cholestyramine binds hormone in the gut lumen and increases faecal loss, thereby accelerating the fall in circulating levels when added to standard therapy. A randomized, double-blind, placebo-controlled trial demonstrated that adding cholestyramine to methimazole and propranolol produced significantly greater reductions in T4, free T4, and T3 over four weeks than the same regimen without it [10]. A usual dose is 4 g every 6–12 hours, given as a short-term adjunct and separated in time from other oral agents to avoid impairing their absorption (evidence: randomized controlled trial).

Thionamides

Where they can be used, thionamides remain the standard means of arresting new hormone synthesis—methimazole or carbimazole at high

divided daily doses, with propylthiouracil reserved for specific situations such as the first trimester of pregnancy or as part of storm management because of its additional inhibition of peripheral conversion [1,6]. The decisive point for this review is that they must not be used after a documented thionamide-induced agranulocytosis or serious hepatotoxicity. It is in exactly these patients and in those in whom thionamides alone do not act quickly enough that lithium becomes a key tool.

Inorganic Iodine

Inorganic iodine (Lugol's solution or saturated solution of potassium iodide, SSKI) acutely inhibits both hormone synthesis and release through the Wolff–Chaikoff effect and reduces thyroid vascularity, which is useful before thyroidectomy. The critical sequencing rule is that, in patients with intact synthetic capacity, iodine should follow thionamide (or be combined with a release-blocking agent) so that the iodine load does not transiently fuel new hormone production; escape from the Wolff–Chaikoff effect also limits the duration of benefit, so iodine is generally introduced 7–10 days before planned surgery [1,4]. Iodine should be avoided where recent iodinated contrast or an iodine-avid process makes loading hazardous.

Lithium Carbonate: Mechanism and Role

Lithium is concentrated within the thyroid follicular cell and produces a marked decrease in the release of preformed thyroid hormone, an effect classically attributed to inhibition of colloid droplet formation and of thyrotropin-stimulated, cyclic-AMP–mediated secretion [7,8]. This release-blocking action was demonstrated in both euthyroid and thyrotoxic subjects in the foundational human studies [8], and the mechanism is the basis of lithium's well-recognized capacity to cause goitre and hypothyroidism during chronic psychiatric use [7]. For thyrotoxicosis, lithium has three attractions: it acts on release rather than synthesis, so it is effective when thionamides cannot be used; it does not depend on iodine handling, so it can be combined with iodine; and it additionally increases intrathyroidal radioiodine retention, which underlies its separate use as an adjunct to radioactive iodine therapy [7]. Its principal limitations are a narrow therapeutic index and the fact that, as monotherapy, it does not reliably render patients euthyroid—an older randomized comparison found it inferior to thionamide therapy—so it is best regarded as a short-term bridge within a multimodal regimen rather than a stand-alone treatment [7,2].

Indications for Adding Lithium in Rapid Preparation

Thionamide intolerance or prior agranulocytosis or hepatotoxicity; inadequate or insufficiently rapid response to thionamide-based therapy when surgery is needed within days to a few weeks; or as a short-term bridge to definitive surgery when iodine alone is insufficient [2,4,7]. A practical immediate-release starting regimen is lithium carbonate 300 mg every 8 hours (about 900 mg/day), with reported acute regimens ranging from roughly 600 to 1000 mg/day in divided doses, titrated to effect and to serum level [4,7]. A pragmatic short-term serum target of approximately 0.4–0.8 mmol/L is sufficient to suppress hormone release while limiting toxicity; surgical-preparation series have reported acceptable safety when levels are kept below approximately 1.0–1.2 mmol/L [4,12] (evidence: case series, small cohorts, and a focused systematic review; no randomized data specific to preoperative use).

Therapeutic Plasma Exchange (Rescue)

When pharmacological measures fail or surgery cannot wait, therapeutic plasma exchange removes protein-bound hormone directly and can rapidly reduce FT4 and FT3 as a bridge to thyroidectomy. Preoperative plasma exchange has been used successfully in patients with severe thyrotoxicosis, thionamide-induced agranulocytosis, and iodine-induced disease, allowing safe subsequent surgery [11,2]. It is resource-intensive, its effect is transient, and it is best timed close to operation; it should be reserved for refractory or life-threatening situations rather than routine preparation (evidence: retrospective series and case reports; recognized apheresis indication for thyroid storm).

Slow-Release Lithium When Immediate-Release Is Unavailable

Immediate-release lithium carbonate is not marketed in every country, and clinicians may have access only to slow-release (sustained- or controlled-release) formulations. The mechanism required for thyrotoxicosis control—inhibition of hormone release and a modest reduction in peripheral conversion—depends on achieving an adequate and sustained serum lithium concentration, not on the speed of the absorption peak [7,8]. This is the pharmacological basis for substituting a slow-release preparation when necessary.

Pharmacokinetically, after a single dose, immediate-release lithium reaches peak plasma concentration at roughly 1–2 hours, whereas

sustained-release forms peak at about 4–5 hours; the sustained-release formulation produces a 30–50 percent reduction in peak concentration with little change in overall exposure (area under the curve) and therefore a smoother concentration–time profile [14]. For preoperative use this translates into two practical consequences: onset of the antithyroid effect may be modestly slower (on the order of an extra day or two), and the more stable levels may reduce peak-related toxicity. Critically, slow-release tablets must never be crushed or split, as this destroys the release mechanism and causes dose dumping with risk of acute toxicity [12,14].

Reported regimens in this context are lithium SR 300 mg three times daily, or 400 mg twice daily depending on the available tablet strength, targeting a serum level of approximately 0.4–0.6 mmol/L—lower than psychiatric maintenance targets—to provide meaningful suppression of hormone release with a wider safety margin [4,12]. Because absorption and the approach to steady state are prolonged, the first level is checked at 48–72 hours rather than at the day-3-to-7 point used for immediate-release dosing. Where onset speed is limiting, the slow-release arm leans more heavily on the faster-acting co-interventions—beta-blockade, glucocorticoids, iodine introduced after lithium, and cholestyramine—to bridge the interval [2,3].

Proposed Operational Protocols

The two protocols below operationalize the foregoing principles. They are intended as structured starting frameworks for inpatient or closely monitored use, not as rigid prescriptions; doses and timing should be individualized and adjusted with endocrinology and, where relevant, nephrology input. Both assume baseline assessment of renal function and electrolytes, thyroid function, an electrocardiogram where cardiac risk exists, a pregnancy test in women of child-bearing potential, and review and where possible withdrawal of agents that raise lithium levels (non-steroidal anti-inflammatory drugs, ACE inhibitors, angiotensin-receptor blockers, and thiazide diuretics) [4,12,14].

Protocol a — Immediate-Release Lithium

Component	Regimen	Purpose / Notes
Beta-Blocker	Propranolol 40–80 Mg PO Q6–8h (Titrate To HR <90/Min); IV Titration Only In Monitored Setting	Symptom And Rate Control; Modest Reduction Of T4→T3 Conversion
Glucocorticoid	Dexamethasone 2 Mg PO/IV Q6–8h Or Hydrocortisone 100 Mg IV Q8h	Reduces Peripheral Conversion; Covers Relative Adrenal Insufficiency
Cholestyramine	4 G PO Q6–12h (Separate From Other Oral Drugs)	Interrupts Enterohepatic Recirculation; Accelerates Hormone Fall
Thionamide (If Not Contraindicated)	Methimazole 30–60 Mg/Day In Divided Doses (Or Carbimazole Equivalent)	Blocks New Synthesis; Omit If Prior Agranulocytosis Or Hepatotoxicity
Lithium Carbonate (IR)	300 Mg PO Q8h (~900 Mg/Day); Titrate To Level	Blocks Release Of Preformed Hormone; Thionamide-Independent
Inorganic Iodine	Lugol's 5–10 Drops PO TID Or SSKI Per Local Protocol, Started After Thionamide / With Lithium, ~7–10 Days Pre-Op	Inhibits Release And Reduces Vascularity; Observe Wolff–Chaikoff Sequencing
Lithium Level Target	Trough (12 H Post-Dose) ~0.4–0.8 Mmol/L; First Level Day 3–7, Then Weekly (Twice Weekly Acutely)	Stop If Level >1.5 Mmol/L Or Toxicity; Reduce Dose If Rising
Monitoring	Creatinine/Egfr And Sodium At Baseline Then ≥Weekly; Tfts Every 3–7 Days; Daily Neuro Checks	Watch For Nausea, Tremor, Ataxia, Confusion
Rescue	Therapeutic Plasma Exchange If Refractory Or Surgery Cannot Wait	Bridge To Thyroidectomy; Transient Effect

Protocol B — Slow-Release Lithium (Target: Surgical Readiness in 5–7 Days)

Day	Action	Notes

Day 0	Baseline Labs/ECG/Weight + Hydration. Start Lithium SR 300 Mg Q8h (Or 400 Mg BD) + Propranolol 40 Mg TID + Hydrocortisone 100 Mg IV Q8h (Then 50 Mg TID) Or Prednisolone 30–40 Mg/Day	Do NOT Crush/Split SR Tablets. Avoid Lithium If Egfr <40, Dehydration, Hyponatraemia, Or Unstoppable NSAID/Acei/ARB Use
Day 1	Continue Lithium SR, Beta-Blocker, Steroid; Monitor Hydration, Heart Rate, Symptoms	Faster-Acting Agents Bridge Slower Lithium Onset
Day 2	Add Inorganic Iodine (≥24 H After Lithium Started): Lugol's 5 Drops TID, Or SSKI, Or IV Iodide If Available/Inpatient	Iodine After Lithium To Respect Release-Block Sequencing
Day 3	Add Cholestyramine 4 G BID (Optional But Helpful)	Accelerates FT4 Decline
Monitoring	Lithium Level At 48–72 H (Target 0.4–0.6 Mmol/L); Urea/Creatinine + Sodium Daily (Inpatient) Or 48-Hourly; ECG If Arrhythmia Risk	If Level >0.8 Mmol/L, Reduce To BD
Day 4–6	Operate When Stable: HR <90/Min, No Agitation/Tremor, No Fever, No New Arrhythmia, FT4 Trending Down (Not Necessarily Normal)	Clinical And Biochemical Readiness Both Documented
Post-Op	Stop Lithium 3–5 Days Post-Op Once Stable; Taper Steroids Over 2–3 Days; Continue Beta-Blocker Until Euthyroid On Replacement	Avoid Abrupt Destabilization

Oncological Context

This compressed approach is most justified where surgical delay carries a concrete oncological or airway cost rapidly progressive or aggressive thyroid malignancy, impending airway compromise from a bulky goitre or tumour, or coincident non-thyroidal cancer requiring urgent resection in a thyrotoxic patient. In such cases the marginal risk of an intensively monitored multimodal preparation is weighed against the risk of losing a curative surgical window [2,4].

Monitoring, Safety, and Drug Interactions

Lithium's narrow therapeutic index makes structured monitoring mandatory. Because lithium is eliminated almost entirely by the kidney and handled in parallel with sodium, any drug or state that reduces renal clearance or depletes sodium raises the level and the risk of toxicity. The most important interacting agents are non-steroidal anti-inflammatory drugs, ACE inhibitors and angiotensin-receptor blockers, and thiazide diuretics; dehydration and hyponatraemia act similarly [12,14]. These should be reviewed and, where feasible, withheld before and during lithium exposure, with the level rechecked after any change.

Early features of toxicity worsening nausea or diarrhoea, coarse tremor, ataxia, drowsiness, and confusion should prompt an immediate level and clinical reassessment; lithium is stopped for severe features or a level above approximately 1.5 mmol/L [12]. A systematic review and meta-analysis of lithium safety confirms that, while chronic use carries renal, thyroid, and parathyroid effects, the acute toxicity profile of short-term, level-guided use is manageable, and serious outcomes are uncommon with appropriate monitoring [13]. For brief preoperative courses, this favourable short-term profile is the relevant consideration, but lithium should still be avoided or used only with specialist input in significant renal impairment and in pregnancy, where it carries specific teratogenic concerns [1,12].

Quality of Evidence and Limitations

The evidence underpinning rapid lithium-based preparation is modest in level. Much of it comprises case series, small retrospective cohorts, and systematic reviews of these, together with older studies that examined lithium chiefly as an adjunct to radioiodine rather than as preoperative therapy [2,7]. A focused 2024 systematic review of second-line perioperative management—incorporating lithium, cholestyramine, glucocorticoids, and plasma exchange found that such regimens enabled surgery without perioperative storm and achieved mean reductions of roughly 50 percent in FT4 and 68 percent in FT3, but the constituent studies were observational and heterogeneous [2]. No randomized controlled trial has tested a lithium-anchored rapid preoperative protocol, and lithium is not endorsed as a first-line, universal recommendation in major guidelines [1].

These protocols should therefore be read as evidence-informed, expert-derived frameworks rather than guideline-mandated pathways. Their strengths are mechanistic coherence—each agent targets a distinct step in hormone economy and a body of consistent, if low-level,

clinical experience supporting efficacy and short-term safety. Their principal weaknesses are the absence of randomized validation, inter-institutional variation in iodine and lithium practice, and a dependence on close monitoring that may not be available in every setting. Prospective registry data or a pragmatic multicentre study comparing rapid multimodal preparation against standard thionamide preparation, with oncological as well as endocrine outcomes, would materially strengthen the evidence base.

CONCLUSION

For the thyrotoxic patient whose surgery cannot safely wait the several weeks that thionamide preparation requires, most pressingly when an oncological window is closing, a structured, multimodal rapid-optimization protocol offers a defensible path to operative safety within days. Lithium carbonate, acting on hormone release through a thionamide-independent mechanism, is the pivotal adjunct in this strategy and can be delivered using either immediate-release or slow-release formulations, the latter extending the approach to countries where immediate-release lithium is unavailable. Combined with beta-blockade, glucocorticoids, inorganic iodine, and bile-acid sequestration, and with therapeutic plasma exchange held in reserve, lithium-based preparation has a coherent rationale and supportive, if low-level, evidence. Given lithium's narrow therapeutic index, the approach demands careful patient selection, attention to drug interactions, and close biochemical and renal monitoring, ideally within a multidisciplinary framework.

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