

Review Article

Treatment of Thyroid Storm in ICU

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DOI: <https://doi.org/10.3329/bccj.v11i2.69189>

Abstract:

Among endocrine emergencies thyroid storm is a very devastating disease. Sometimes patient presents with cardiovascular or neurological disorder; admits in general medical unit other than ICU. But all Thyroid storm patients should be treated in medical ICU. Delay in diagnosis and/or treatment increases morbidity and mortality. Presentation usually with severe hyperthyroid with other systemic dysfunction. Liver function test usually altered. It has got definite diagnostic criteria. Burch HB, Wartofsky L has a scoring scale. Temperature, involvement of central nervous system, Gastro-intestinal or Liver, Heart rate, Atrial fibrillation and precipitating factors give definite scoring system and ideas for prognosis. Treatments depend on severity and associated co-morbidities. Propylthiouracil or Carbimazole or Methimazole should be started early. Propranolol/beta blocker, Digoxin, Saturated Solutions of Potassium Iodide, Hydrocortisone, Antibiotics and IV fluids are essential. Rarely treated with Cholestyramine, Lithium etc. Plasmapheresis is a lifesaving procedure.

Key words: Thyroid storm, Medical ICU.

Introduction

Endocrine emergencies represent a group of potentially life-threatening conditions that are frequently overlooked, resulting in delays in both diagnosis and treatment and increases morbidity and mortality^{1,2}. True incidence of primary endocrine emergencies is not well defined, which is likely because the disease process is often not recognized. Although endocrine emergencies are often encountered in patients with a known endocrinopathy, the emergency may be the initial presentation in previously undiagnosed individuals³. Among the common endocrine emergencies: thyroid storm, myxedema coma, diabetic ketoacidosis (DKA), pituitary apoplexy and adrenal crisis are frequently encountered^{4,5}. From the thyroid emergencies Thyroid storm is reviewed here.

Malignant or critical thyrotoxicosis, thyroid storm, is a life-threatening medical emergency in which excessive concentrations of thyroid hormone produce organ dysfunction. It is an uncommon manifestation of hyperthyroidism, occurring in less than 10% of patients hospitalized for thyrotoxicosis⁶. However, it may be the presenting symptom of the condition and, if untreated, is associated with 80% to 90% mortality. Even with treatment, mortality from thyroid storm exceeds 20%³. Recognition and immediate management is important in preventing the high morbidity and mortality associated with this disease.

A spectrum of thyroid dysfunction exists. Hyperthyroidism, or thyrotoxicosis, refers to disorders that result from overproduction and release of hormone from the thyroid gland. Thyrotoxicosis refers to any cause of excessive thyroid hormone concentration, whereas malignant thyrotoxicosis, or thyroid storm, represents an extreme manifestation of thyrotoxicosis with resultant end-organ dysfunction or death^{7,8}.

In real life due to increased awareness of the physician and patients now a days the incidence of thyroid storm become very rare. Death rate still remains high due to late presentation and delay in diagnosis. Still in Intensive Care Unit (ICU), High Dependency Unit (HDU) or Coronary Care Unit (CCU) some of the hyperthyroid/Thyrotoxic patients seems to be care of thyroid storm but differential remains, severe hyperthyroidism with sepsis/septic shock, infection with fast AF, sepsis with hepatopathy, hyperthyroidism with heart failure etc.

Treatment

Thyroid storm poses diagnostic and therapeutic challenges. Treatment is aimed at halting the thyrotoxic process at all levels. Prompt recognition and treatment is essential for successful management and is paramount to decreasing the high mortality associated with this disease.

The treatment of thyroid storm involves 3 critical fundamentals. First, supportive care should be provided to minimize the secondary effects of organ failure. This should include respiratory and hemodynamic support and treatment of hyperthermia. Second, identification and treatment of the precipitating event is warranted to prevent further progression of disease. Third, and most critical, the release and effects of circulating thyroid hormone must be blocked. Inhibition of the peripheral conversion of Thyroxine (T4) to Triiodothyronine (T3) helps attenuate the effects of thyroid hormone.

Thyroid hormone release can be reduced by the administration of iodinated contrast, and corticosteroids. Hydrocortisone 100

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mg given intravenously every 8 hours has been shown to improve outcomes in patients. Steroid therapy is also beneficial, considering the common association with adrenal insufficiency. Iodine acts by inhibiting hormone release but should not be given until 1 hour after propylthiouracil (PTU) or anti-thyroid drug (ATD) administration. In refractory cases, plasmapheresis, plasma exchange, and peritoneal hemodialysis can be used to remove circulating thyroid hormone. With appropriate treatment, clinical and biochemical improvement are typically seen within 24 hours. Full recovery usually occurs within a week of therapy.

Treatment of the thyroid storm, starts with full support of the patient in an intensive care unit (ICU) since the mortality rate of thyroid storm is substantial. The therapeutic options for thyroid storm are expanded from those used for uncomplicated hyperthyroidism, with additional drugs often used such as glucocorticoids and an iodine solution, and the standard drugs are given in higher doses and with more frequent dosing. Mortality varies with presentation and severity with facilities. In one series mortality in a tertiary care center is 8%. In another series mortality was 17 percent in the ICU and 22 percent 6 months after discharge from hospital^{3,31}.

The principles of treatment outlined below are based upon clinical experience and case studies since there are no prospective studies. They are frequently also applied to patients with severe hyperthyroidism who do not fully meet the criteria for thyroid storm. The therapeutic regimen typically consists of multiple medications, each of which has a different mechanism of action:

For patients with clinical features of thyroid storm or with severe thyrotoxicosis who do not fully meet the criteria for thyroid storm (ie, impending storm), start immediate treatment with a beta blocker (propranolol) in a dose to achieve adequate control of heart rate, typically 60 to 80 mg orally every four to six hours, with appropriate adjustment for heart rate and blood pressure and either Propylthiouracil (PTU) 200 mg every four hours or methimazole (20 mg orally every four to six hours). PTU is favored over methimazole because of PTU's effect to decrease T4-to-T3 conversion. One hour after the first dose of thionamide is taken, we administer iodine {saturated solution of potassium iodide (SSKI), 5 drops orally every six hours or Lugol's solution, 10 drops every eight hours}. The administration of iodine should be delayed for at least one hour after thionamide administration to prevent the iodine from being used as substrate for new hormone synthesis in patients with toxic adenoma or toxic multinodular goiter (since the etiology of the thyrotoxicosis is frequently uncertain at the time of admission).

For patients with clinical features of thyroid storm, administer glucocorticoids (hydrocortisone, 100 mg intravenously every eight hours). Cholestyramine(4 g orally four times daily) may also be of benefit in severe cases to reduce enterohepatic recycling of thyroid hormones.

Supportive therapy and recognition and treatment of any precipitating factors (eg, infection), in addition to specific therapy directed against the thyroid, may be critical to the

final outcome. Many patients require substantial amounts of fluid, while others may require diuresis because of congestive heart failure. Digoxin and beta blocker requirements may be quite high because of increased drug metabolism as a result of hyperthyroidism. Infection needs to be identified and treated, and hyperpyrexia should be aggressively corrected. Acetaminophen should be used instead of aspirin since the latter can increase serum free T4 and T3 concentrations by interfering with their protein binding.

Propranolol, PTU/Methimazole can be administered through a nasogastric tube if not taking orally, even per rectally.

Individual drug

Beta Blockers: For patients with thyroid storm or severe thyrotoxicosis, start immediate treatment with a beta blocker (typically propranolol in a dose to achieve adequate control of heart rate, 60 to 80 mg orally every four to six hours, with appropriate adjustment for heart rate and blood pressure). In one guideline, its recommend that, esmolol has advantages over propranolol because of increased mortality in patients with congestive heart failure treated with propranolol. In patients with Asthma or COPD, cardio selective beta blockers such as metoprolol, bisoprolol or atenolol could be considered, but this should be done carefully. In some patients with severe asthma in whom beta blockers might be contraindicated, rate control can be achieved with calcium-channel blockers such as diltiazem.

Beta blockers should be used with extreme caution if the patient has decompensated heart failure with systolic dysfunction or other contraindications to beta blockade (eg, asthma or chronic obstructive pulmonary disease, severe peripheral vascular disease). It is important to note, however, that control of tachycardia may lead to improvement in cardiac function.

Propranolol can be given intravenously, but this should only be done in a setting where hemodynamics can be monitored. The intravenous dose is 0.5 to 1 mg over 10 minutes followed by 1 to 2 mg over 10 minutes every few hours. Higher doses may occasionally be required, but care should be taken to avoid hypotension and aggravation of existing heart failure. As an alternative to intravenous administration, propranolol can be given orally or via nasogastric tube in a dose to achieve adequate control of heart rate, typically 60 to 80 mg orally every four to six hours. When transitioning from intravenous to oral / nasogastric treatment, intravenous therapy may need to be continued until adequate effectiveness of the oral / nasogastric treatment is ascertained.

An alternative regimen is to utilize the short-acting beta blocker esmolol. A loading dose of 250 to 500 mcg/kg is given, followed by an infusion at 50 to 100 mcg/kg per minute. This regimen permits rapid titration of the drug to achieve adequate beta blockade while minimizing adverse reactions.

Anti-thyroid Medication (Thionamides): Thionamides block de novo thyroid hormone synthesis within one to two hours after administration. However, they have no effect on

the release of preformed hormone from the thyroid gland. For patients with thyroid storm or severe thyrotoxicosis, it is recommended to start immediate treatment with either PTU 200 mg every four hours or methimazole (20 mg orally every four to six hours). Carbimazole, a third drug that is metabolized to methimazole/carbimazole (20-60 mg in 3-4 divided dosage).

- PTU for the acute treatment of life-threatening thyroid storm in an ICU setting, where it can be administered regularly every four hours. PTU, but not methimazole, blocks T4-to-T3 conversion, and T3 levels drop by approximately 45 percent within 24 hours after PTU but only 10 to 15 percent within 24 hours after methimazole.^{9,10}
- Methimazole/carbimazole may be preferred for severe, but not life-threatening, hyperthyroidism because methimazole has a longer duration of action and, after weeks of treatment, results in more rapid normalization of serum T3 compared with PTU and because methimazole is less hepatotoxic.

Patients started on PTU in the ICU should be transitioned to methimazole before discharge from the hospital. In Japan, methimazole is preferred over PTU, and in a retrospective study of 356 patients, there was no difference in mortality or disease severity in patients receiving methimazole or PTU.^{9,10}

The dose of thionamide given to patients with thyroid storm is likely higher than that required to completely block thyroid hormone synthesis. Both the substantial mortality associated with thyroid storm and the possibility of poor absorption because of concurrent gastrointestinal dysfunction have been used to justify the higher dose. Its advocated typically to administer 200 mg of PTU every four hours or 20 mg of methimazole/carbimazole 20-30 mg every four to six hours, orally or via nasogastric tube.

Common Side Effects of ATD (Anti Thyroid Drugs):

Both methimazole and PTU can cause pruritus, rash, urticaria, arthralgias, arthritis, fever, abnormal taste sensation, nausea, or vomiting in some cases.

Agranulocytosis is rare (0.1-0.5 %), but few patients may have neutropenia prior to ATD in case of GD. So, its wise to have a CBC prior to start ATD.

Hepatotoxicity is rare. PTU can cause fulminant hepatic failure. Although Carbimazole and also Methimazole can induce liver enzymes, but severe toxicity is less frequent than PTU.

It is important to measure liver function tests prior to starting a thionamide since hyperthyroidism itself can cause elevations in transaminases and alkaline phosphatase, which normalize in most patients with thionamide treatment.

Patients with thionamide side-effects: Although thionamide toxicity is uncommon, some patients are unable to continue thionamides because of rare side effects such as agranulocytosis or hepatotoxicity or because of rash. Thyroid storm has been reported in patients with Graves' disease after

discontinuation of thionamides due to agranulocytosis or hepatotoxicity. In such patients who require urgent treatment of hyperthyroidism, thyroidectomy is the treatment of choice. Patients who are to undergo surgery require preoperative treatment of thyrotoxicosis. Treat with beta blockers (if not contraindicated, propranolol in a dose to achieve adequate control of heart rate, typically 60 to 80 mg every four to six hours), glucocorticoids to inhibit conversion of T4 to T3 (eg, dexamethasone, 1 to 2 mg every six hours), bile acid sequestrants (eg, cholestyramine 4 g orally four times daily) to reduce enterohepatic circulation of thyroid hormone, and, in patients with Graves' disease, iodine (SSKI, 5 drops [20 drops/mL, 50 mg iodide/drop] orally every six hours or Lugol's solution, 10 drops [20 drops/mL, 6.25 mg iodine/drop] every eight hours).¹¹

Continue treatment for up to five to seven days. Surgery should not be delayed for more than 8 to 10 days, because of a phenomenon called escape from the Wolff-Chaikoff effect. Large doses of exogenous iodine inhibit the organification of iodine in the thyroid gland (the Wolff-Chaikoff effect). However, this effect is transient. The iodide transport system is able to adapt to higher concentrations of iodine, allowing thyroid hormone synthesis to proceed, with potential exacerbation of thyrotoxicosis.

In case reports, when traditional therapy has not been successful, plasmapheresis has been used to prepare patients with thyroid storm for thyroid surgery. Iodinated contrast agents have also been used to prepare hyperthyroid patients for urgent surgery, but they are no longer available in most countries.

Iodine : For patients with thyroid storm or severe thyrotoxicosis, administer iodine one hour after the first dose of thionamide is taken. The administration of iodine should be delayed for at least one hour after thionamide administration to prevent the iodine from being used as substrate for new hormone synthesis in patients with toxic adenoma or toxic multinodular goiter (since the etiology of the thyrotoxicosis is frequently uncertain at the time of admission).

Iodine-containing solutions have traditionally been utilized for the treatment of thyroid storm since iodine blocks the release of T4 and T3 from the gland within hours. Oral doses are potassium iodide-iodine (Lugol's) solution, 10 drops (6.25 mg iodide/iodine per drop [0.05 mL]) three times daily or SSKI, 5 drops (50 mg iodide/drop [0.05 mL]) every six hours.¹² There is no standard intravenous iodide preparation, but it has been suggested that 10 drops of Lugol's solution can be directly added to intravenous fluids since it is sterile. The iodine solution can also be given rectally. Although iodine is typically well tolerated, local esophageal or duodenal mucosal injury and hemorrhage have been reported after oral administration of Lugol's solution (960 mg iodine/day) for the treatment of thyroid storm. These solutions can be irritating and should be diluted in 240 mL or more of beverage and taken with food.

Iodinated radiocontrast agents : Iopanoic acid and other iodinated radiocontrast agents used for oral cholecystography

have been used to treat hyperthyroidism, but there are little published data on their efficacy in thyroid storm. They are, however, potent inhibitors of T4-to-T3 conversion, and the release of iodine in pharmacologic quantities from these agents has the additional benefit of blocking thyroid hormone release. They have been extremely useful in treating severe hyperthyroidism and in preparing hyperthyroid patients for

urgent surgery.¹² If available, these agents can be given to patients with severe hyperthyroidism at a dose of 0.5 to 1 g once daily. Because they are iodinated, they should be given at least one hour after the thionamide to prevent the iodine from being used as substrate for new hormone synthesis. But iodinated contrast agents are not available in US and many countries now a days.

Table II: Commonly used drugs in Thyrotoxicosis

| DRUG | DOSES | Remarks |
|----------------|------------------------|---|
| PTU | 200 mg 4 hourly | For life threatening Thyroid Storm Blocks new hormone synthesis Blocks T4 to T3 conversion |
| Methimazole | 20 mg every 6 hours | Non-life threatening disease Blocks new hormone synthesis |
| Carbimazole | 20-mg every 6 hours | Same as Methimazole |
| Propranolol | 60-80 mg every 6 hours | Blocks T4 to T3 conversion Care of heart failure Alternate: Esmolol |
| SSKI | 5 drops every 6 hours | Blocks new hormone synthesis Do not start until 1 hour from ATD Alternate: Lugols iodine: 10 drops 8 hourly |
| Hydrocortisone | 100 mg every 8 hours | Blocks T4 to T3 conversion Prophylaxis against Adrenal insufficiency, Alternate: Dexamethasone Care of Blood glucose & Potassium |

Glucocorticoids — For patients with convincing clinical features of thyroid storm, administer glucocorticoids (hydrocortisone, 100 mg intravenously every eight hours). In contrast, its recommended that, do not routinely use glucocorticoids in patients with severe, but not life-threatening, hyperthyroidism.

Glucocorticoids reduce T4-to-T3 conversion. In addition, they may have a direct effect on the underlying autoimmune process, if the thyroid storm is due to Graves' disease, and treat potentially associated limited adrenal reserve¹³. Because of the high mortality rate of thyroid storm, their use is commonly recommended by experts, although data are limited. In a retrospective study based on a claims database (811 ICU admissions for thyroid storm between 2013 and 2017), 600 patients received glucocorticoids and 211 did not. There was no change in hospital mortality or mortality 30 days after discharge¹³. Glucocorticoid use associated with increased use of insulin for diabetics.

Bile acid sequestrants — Thyroid hormones are metabolized in the liver, where they are conjugated with glucuronide and sulfate, and the conjugation products are excreted in the bile.

Free thyroid hormones are released in the intestine and are reabsorbed. Bile acid sequestrants have been found to reduce thyroid hormone levels in thyrotoxic patients by interfering with enterohepatic circulation and recycling of thyroid hormone¹⁴. They are useful adjunctive therapy in patients with thyroid storm, particularly in patients who are intolerant of thionamide.

- **Plasmapheresis** – Plasmapheresis has been tried when traditional therapy has not been successful. Plasmapheresis removes cytokines, antibodies, and thyroid hormones from plasma^{15,16}. In one case report, a woman with Graves' disease and methimazole-induced agranulocytosis developed thyroid storm after methimazole was discontinued. Treatment with plasmapheresis resulted in marked improvement in thyrotoxicosis within three days, allowing thyroidectomy for definitive therapy. In a series of three patients who had therapeutic plasma exchange for thyroid storm preoperatively, free T4 levels were reduced on average by 21 percent after each treatment and by 55 percent after four treatments.

- **Lithium** – Lithium has also been given to acutely block the release of thyroid hormone. However, its renal and neurologic toxicity limit its utility.
- **Digoxin**: may be necessary for AF, arrhythmia or heart failure with thyroid storm.

Long-term management: After the evidence of clinical improvement (defervescence, resolution of central nervous system and cardiovascular manifestations), iodine therapy can be discontinued, and glucocorticoids tapered and discontinued. Beta blockers can be withdrawn but only after thyroid function tests have returned to normal. The dose of thionamides should be titrated to maintain euthyroidism. PTU, if given, should be switched to methimazole because of methimazole's better safety profile and better compliance rates.

In patients with Graves' disease, definitive therapy with radioactive iodine or thyroidectomy is important to prevent a recurrence of severe thyrotoxicosis. Radioiodine therapy as first choice for definitive therapy for hyperthyroidism in the absence of moderate to severe orbitopathy, given its lower cost and lower complication rate compared with surgery. If the patient received iodine within a few weeks of planned radioiodine treatment, a radioiodine uptake should be obtained to calculate the radioiodine treatment dose rather than using fixed-dose radioiodine treatment. Surgery is an option, especially for patients with hyperthyroidism due to a very large or obstructive goiter.

SUMMARY:

Thyroid storm is a rare, life-threatening condition characterized by severe or exaggerated clinical manifestations of thyrotoxicosis. Although thyroid storm can develop in patients with longstanding untreated hyperthyroidism (Graves' disease, toxic multinodular goiter, solitary toxic adenoma), it is often precipitated by an acute event such as thyroid or nonthyroidal surgery, trauma, infection, an acute iodine load, or parturition.

Patients with thyroid storm typically have an exaggeration of the usual symptoms of hyperthyroidism. The classical symptoms of thyroid storm include tachycardia, hyperpyrexia, central nervous system dysfunction (agitation, delirium, psychosis, stupor, or coma), and gastrointestinal symptoms (nausea, vomiting, abdominal pain). Physical examination may reveal goiter, ophthalmopathy (in the presence of Graves' disease), lid lag, hand tremor, and warm and moist skin.

Thyroid function tests show frank hyperthyroidism (suppressed thyroid-stimulating hormone [TSH], elevated free thyroxine [T4] and triiodothyronine [T3]) generally comparable with that in patients with uncomplicated overt hyperthyroidism.

The diagnosis of thyroid storm is based upon the presence of severe and life-threatening symptoms (hyperpyrexia, cardiovascular dysfunction, altered mentation, CV manifestations, dehydration, increased liver enzymes) in a patient with biochemical evidence of hyperthyroidism

(elevation of free T4 and/or T3 and suppression of TSH). There are no universally accepted criteria or validated clinical tools for diagnosing thyroid storm. In one scoring system (bellow: Bruce-Wartofsky score), a score of 45 or more is highly suggestive of thyroid storm, whereas a score below 25 makes thyroid storm unlikely.

The therapeutic options for thyroid storm are expanded from those used for uncomplicated hyperthyroidism, with additional drugs typically used, such as glucocorticoids and iodine solution (eg, saturated solution of potassium iodide [SSKI]), and standard drugs are given in higher doses and more frequently. In addition to specific therapy directed against the thyroid, supportive therapy in an ICU and recognition and treatment of any precipitating factors is essential since the mortality rate of thyroid storm is substantial (10 to 30 percent).

For patients with clinical features of thyroid storm, start immediate treatment with a beta blocker (propranolol in a dose to achieve adequate control of heart rate, typically 60 to 80 mg orally every four to six hours), a thionamide, and glucocorticoids (hydrocortisone, 100 mg intravenously every eight hours). One hour after a thionamide is given, we administer iodine (SSKI, 5 drops [20 drops/mL, 50 mg iodide/drop] orally every six hours or Lugol's solution, 10 drops [20 drops/mL, 6.25 mg iodine/drop] every eight hours). Bile acid sequestrants (cholestyramine, 4 g orally four times daily) may also be of benefit in severe cases to decrease enterohepatic recycling of thyroid hormones.

For patients with life-threatening thyroid storm admitted to an ICU, propylthiouracil (PTU) (200 mg orally every four hours) rather than methimazole/carbimazole is recommended as initial therapy. PTU blocks T4-to-T3 conversion and results in lower serum T3 levels for the first several days of treatment. However, for severe, but not life-threatening, hyperthyroidism, methimazole (20 mg every six hours) may be preferred because of its longer half-life, lower risk of hepatic toxicity, and because it ultimately restores euthyroidism more quickly than PTU. Patients initially treated with PTU should be transitioned to methimazole before discharge from the hospital.

For patients with contraindications to thionamide who require urgent correction of hyperthyroidism, surgery is the treatment of choice. Patients who are to undergo surgery require preoperative treatment of thyrotoxicosis. Treat with beta blockers (if not contraindicated, propranolol 60 to 80 mg every four to six hours), glucocorticoids to inhibit conversion of T4 to T3 (eg, dexamethasone, 1 to 2 mg every six hours), bile acid sequestrants (eg, cholestyramine 4 g orally four times daily), and, in patients with Graves' disease, iodine (SSKI, 5 drops [50 mg iodide/drop] orally every six hours or Lugol's solution, 10 drops [6.25 mg iodide/iodine per drop] every eight hours). We continue treatment for up to five to seven days.

After the clinical manifestations of thyroid storm are improved, long-term therapy is required to prevent a recurrence of severe thyrotoxicosis. For definitive therapy of

patients with hyperthyroidism secondary to Graves' disease, toxic multinodular goiter, or toxic adenoma, radioiodine therapy is first choice in the absence of moderate to severe Graves' orbitopathy, given its lower cost and lower complication rate than surgery. Surgery is an option, especially for patients with hyperthyroidism due to a very large or obstructive goiter.

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