

Review Article and Clinical Experience: THYROID STORM: A LIFE-THREATENING THYROTOXICOSIS Therapeutic Clinical Experiences with Formula TS 41668-24-6

Askandar Tjokroprawiro

Airlangga University School of Medicine
Diabetes and Nutrition Center,
Dr. Soetomo Teaching Hospital, Surabaya

ABSTRACT

Thyroid Crisis (TC) or Thyroid Storm (TS) is an acute, life-threatening, thyroid hormones-induced hypermetabolic state involving multiple systems in patients with thyrotoxicosis or those who are previously unrecognized thyrotoxicosis. The Burch-Wartofsky-Point Score (BWPS) has been widely used in Surabaya as a device of diagnostic criteria for TS. Formula TS 41668-24-6 has been used as specific practical guideline in the treatment of TS and its therapeutic clinical outcomes. The description of this Formula can be followed below. "4" means: 400 mg loading dose of PTU, with maintenance dose: 100-200 mg PTU every 4 hours. PTU is given to inhibit TH synthesis and to inhibit the conversion of T4 to T3. Alternatively, methimazole: 40 mg as a loading dose can be given, with maintenance dose 10 mg every 4 hours. "1" means: PTU should be administered at least 1 hour before giving iodine to establish blockade of hormone synthesis. The first "6" means: 6 drops of Lugol's solution or SSKI every 6 hours to inhibit TH release from thyroid gland and should be evaluated after 6 days. The second "6" means: administration 10-40mg propranolol every 6 hours to decrease heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Reevaluation of propranolol administration should be done after 6 days. "8" means: 100-200 mg IV hydrocortisone hemisuccinate every 8 hours to block the conversion of T4 to T3. Stress dose are required to replace accelerated production and degradation of cortisol induced by TH. "24" means: with adequate thyroid-suppressive therapy and sympathetic blockade, clinical improvement should occur within 24 hours. The last "6" means: adequate therapy should resolve the TS within 6 days.

Keywords: *Thyroid Crisis (TC), Thyroid Storm (TS), thyrotoxicosis, The Burch-Wartofsky-Point Score (BWPS), Formula TS 41668-24-6*

Correspondence: Askandar Tjokroprawiro, Airlangga University School of Medicine, Diabetes and Nutrition Center, Dr. Soetomo Teaching Hospital, Jl Mayjen Mustopo 6-8, Surabaya, phone: 62-31-5501625

INTRODUCTION

Thyroid Storm (TS) or Thyroid Crisis (TC) usually develops after some specific precipitating event such as infection, sepsis, trauma, cerebrovascular accident, or radioactive iodine therapy, etc (Table 1). Thyroid Storm may present as so called masked or apathic thyrotoxicosis (Ghobrial et al 2002), in which case signs and symptoms may be subtle, or not previously diagnosed with thyrotoxicosis (Hughes et al 2003). The clinical picture reflexes to severely exaggerated effects of thyroid hormones (THs). Heat intolerance and diaphoresis are common in simple thyrotoxicosis but manifest as hyperpyrexia in TS. The temperature consistently exceeds 38.5°C, but frequently exceeds 40°C. Excessive sweating may frequently exist. In addition to the thermoregulatory dysfunction, other cardinal systems, such as CNS, Gastrointestinal-Hepatic System, and Cardiovascular System are fundamentally involved. Diagnosis of TS is primarily clinical, and no

specific laboratory tests are available. However, Burch-Wartofsky Point Score (BWPS) can be used as diagnostic criteria for TS (Burch et al. 1993, Tietgens et al. 1995). Formula 41668 (Tjokroprawiro 2002) and the revised Formula TS 41668-24-6 (Tjokroprawiro 2005) have been routinely used in Surabaya as guidelines of specific treatment of TS and its therapeutic clinical outcomes.

Thyroid Storm is an acute, life-threatening emergency with extremely high mortality (90%) in USA if early diagnosis is not made and the patients is left untreated. However, with better control of thyrotoxicosis and early treatment of TS, the mortality has decreased to less than 20%. The aim of this paper is to transfer a practical knowledge of TS (background and rationale therapy with Formula TS 41668-24-6) to GPs, residents, internists, candidates of endocrinologists, and associated specialists.

PATHOGENESIS OF THYROID STORM OR THYROID CRISIS

The following hypotheses or theories of the pathogenesis of thyroid storm (TS) have been proposed (Tietgens et al 1995; Singhal 2003).

1. The rapidity with which the hormone levels rise may be more important than the absolute levels in determining the clinical presentation. One mechanism for a sudden change in hormone levels would be a change in the levels of the binding protein (Colebunders et al. 1984). This has been noted to occur postoperatively and in patients with systemic nonthyroidal illness. The production of thyroid hormone-binding inhibitor(s), which has been demonstrated in the sera from several patients with nonthyroidal systemic illnesses, could decrease the binding affinity of thyroid hormones and increase free hormone levels. Hughes et al (2003) reported thyroid storm, a 55-year-old woman, following a tibial fracture, who was not previously diagnosed with hyperthyroidism, experienced a cardiac arrest secondary to thyroid storm.
2. Adrenergic receptor activation is another hypothesis. In this theory, sympathetic nerves innervate the thyroid gland, and catecholamines can stimulate TH synthesis. This increased TH then increases the density of beta-adrenergic receptors, thereby enhancing the effect of catecholamines. This hypothesis is supported by the dramatic response of TS to beta blockers and the occurrence of TS after accidental ingestion of adrenergic drugs such as pseudoephedrine.
3. Another hypothesis suggests a rapid rise of hormone levels as the pathogenic source. A drop in binding proteins, which might occur postoperatively, might cause a sudden rise in free hormone levels. A rapid rise in TH levels also may occur when the gland is manipulated during surgery or by vigorous palpation during physical examination.
4. The last proposed theories include: tissue tolerance to THs; presence of a unique catecholamine like substance in thyrotoxicosis; a direct sympathomimetic effect of TH as a result of its structural similarity to catecholamines.

In general, FT3 and FT 4 correlate poorly with severity of condition: condition is essentially an inability of end-organs to modulate their response to excess thyroid hormone.

LABORATORY STUDIES

1. Never forget that the diagnosis for thyroid storm is clinically based; no laboratory tests are diagnostic. If the patient's clinical picture is consistent with thyroid storm, never delay treatment to await laboratory confirmation of thyrotoxicosis.
2. Thyroid Studies
 - a. Result of thyroid studies usually are consistent with hyperthyroidism and are useful only if the patient has not been diagnosed previously.
 - b. Test results may not come back quickly and usually are unhelpful for immediate management
 - c. Usually findings include elevated triiodothyronine (T3) and thyroxine (T4), elevated free T4, increased T3 resin uptake, suppressed TSH, and an elevated 24-hour iodine uptake. TSH is not suppressed if the etiology is excess TSH secretion.
 - d. CBC reveals mild leukocytosis, with a shift to the left.
 - e. Liver function tests commonly show nonspecific abnormalities such as elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatin kinase, alkaline phosphatase, and serum bilirubin.
 - f. Blood gases, electrolytes, and urinalysis testing may be performed to assess and monitor short-term management.

KNOWN PRECIPITANTS OF THYROID CRISIS OR THYROID STORM

In most cases of Thyroid Crisis (TC) or Thyroid Storm (TS), precipitating events (precipitants) can be identified. Known precipitants of TS (Burch et al. 1993, Tietgens et al. 1995, Hall et al. 1999, Turner et al 2003, Greenspan et al. 2004) can be seen in Table 1. In thyroid storm, the fever and tachycardia tend to be out of proportion to the illness.

Table 1. 18 Known Precipitants of Thyroid Storm
(Burch et al. 1993, Tietgens et al. 1995, Hall et al. 1999, Turner et al. 2003, Greenspan et al. 2004)

Infection	Toxemia of pregnancy
Surgery – thyroid, nonthyroidal	Parturition
Iodinated contrast dyes	Severe emotional stress
Withdrawal of antithyroid drug therapy	Pulmonary embolism
Radioiodine therapy	Cerebral vascular accident
Thyroid hormone ingestion	Bowel infarction
Diabetic Ketoacidosis or Hypoglycemia	Trauma: fracture, etc
Amiodarone	Tooth extraction
Congestive heart failure	Vigorous palpation of the thyroid gland

EFFECT OF PREGNANCY ON THYROID FUNCTION

(Turner et al. 2003, Summarized: 2005)

A. Normal

1. Thyroid Stimulating Hormone (TSH) within normal limit in pregnancy. However, suppressed in 13.5% in 1st trimester, 4.5% in 2nd trimester and 1.2% in 3rd trimester due to hCG thyrotropic effect. Positive correlation between FT4 and hCG levels and negative correlation between TSH and hCG levels in first half of pregnancy.
2. Thyrotropin Releasing Hormone (TRH) Normal

B. Decreased: Iodide Stores. Decrease, due to increased renal clearance and transplacental transfer to fetus.

C. Increased

1. Thyroid Size. Increase in thyroid volume by 10-20% due to hCG stimulation and relative iodide deficiency
2. Thyroglobulin. Increase corresponds to rise in thyroid size
3. Thyroid Binding Globulin (TBG). Twofold increase in concentration as a result of reduced hepatic clearance and increased synthesis stimulated by estrogen. Concentration plateaus at 20 weeks of gestation, and falls again post partally.
4. Total T4 and T3. Increased concentrations, corresponding to rise in TBG
5. Free T4 and T3. Small rise in concentration in the first trimester due to hCG stimulation then fall into normal range.

AMIODARONE AND THYROID FUNCTION

(Greenspan et al. 2004, Summarized: 2005)

Amiodarone contains 39% iodine by weight. On a dose of amiodarone between 200-600 mg daily, 7-21 mg

iodine is made available each day (the optimal daily iodine intake is 150-200 µg). Amiodarone is distributed in several tissues from where it is slowly released. Importantly, the terminal elimination half-life of amiodarone averaged 52.6 days with a standard deviation 23.7 days. Abnormalities of thyroid function occur in up to 50% of patients. In the UK and USA, 2% of patients develop thyrotoxicosis (AIT = amiodarone-induced thyrotoxicosis) and about 13% develop hypothyroidism (AIH = amiodarone-induced hypothyroidism). However, AIT occurs more frequently in regions with low iodine intake. AIT may present several months after discontinuing the drug (long half-life); AIH is commoner in women and in patients with thyroid auto antibodies. Thyroid function tests should be monitored every 6 months in amiodarone treated patients. The high iodine content of amiodarone may inhibit TH synthesis and release of TH causing AIH, or loading to iodine-induced thyrotoxicosis. Thyrotoxicosis resulting from iodine excess (induced TH synthesis) is referred to as AIT Type-I, whereas thyrotoxicosis due to a direct toxic effects of amiodarone is referred as to AIT Type-II (Table 2). Drug induced destructive thyroiditis results in leakage of thyroid hormones from damaged follicles into the circulation, and like subacute thyroiditis can be followed by a transient hypothyroid state before euthyroidism is restored.

Management of Amiodarone-induced Thyrotoxicosis (Greenspan et al. 2004, Summarized: 2005)

1. Stop amiodarone if possible
2. Institute β-blocker therapy if possible
3. Antithyroid drugs: Tapazole, 40 - 60 mg/dl
4. Potassium perchlorate, 200 mg every 6 hours
5. Cholestyramine or Colestipol, 20 - 30 g/d
6. Prednisone, 40 mg/d, for acute thyroiditis (Monitor IL - 6 levels)
7. Thyroidectomy

Table 2. Characteristics of Amiodarone induced Thyrotoxicosis

	AIT Type-I	AIT Type-II
Aetiology	Iodine toxicity	Thyroiditis
Signs of clinical thyroid disease	Yes	No
Goiter	Frequent	Infrequent
Thyroid antibodies	Positive	Negative
Radioiodine uptake	Normal	Decreased
Thyroglobulin	Normal or slightly elevated	Very elevated
Serum IL-6	Normal	Very elevated
Late hypothyroidism	No	Possible
Vascularity (Doppler)	Increased / Normal	Reduced

DIAGNOSTIC CRITERIA FOR THYROID STORM

The diagnosis of thyroid storm (TS) is clinically based, and there is no one specific set of diagnostic criteria that can be used reliably to make the diagnosis in all patients. Burch and Wartofsky (1993) have devised a diagnostic point scale (Burch-Wartofsky Point Score = BWPS) to help distinguish uncomplicated thyrotoxicosis, impending TS, and established TS on a semi quantitative basis (Table 3).

There are no laboratory criteria to diagnose TS, although patients have findings consistent with thyrotoxicosis. As seen in Table 3, in patients with severe thyrotoxicosis, points are assigned to the highest weighted description applicable in each category and scores totaled. When it is not possible to distinguish the effects of an inter current illness from those of the severe thyrotoxicosis per se, points are awarded such as to favor the diagnosis of storm and hence empiric therapy. A score of 45 or greater is highly suggestive of thyroid storm; a score of 25-44 is suggestive of impending storm, and a score below 25 is unlikely to represent thyroid storm. In thyroid storm: Fever and Tachycardia tend to be the 2 most important points.

MANAGEMENT OF THYROID STORM

The management of thyroid storm (TS) can be categorized into Supportive Care and Specific Measures (Burch et al. 1993, Tietgens et al. 1995, Tjokropawiro 2002, 2005, Belchet et al. 2003, Hughes et al. 2003, Singhal et al. 2003, Turner et al. 2003, Greenspan et al. 2004)

SUPPORTIVE CARE OF THYROID STORM

The general supportive therapy may include:

1. Fluid balance, Glucose Infusion for nutrition
2. Oxygen
3. Cardio respiratory status
4. Cooling Blanket
5. Acetaminophen (Avoid Aspirin: since this drug will displace T4 from TBG, resulting in an increase in FT4. Chlorpromazine (50-100 mg I.M) can be used to treat agitation and because of its effect in inhibiting central thermoregulation, hence, it may be useful in treating hyperpyrexia.
6. Phenobarbital. It may be a useful sedative since it stimulates T4 metabolism via the hepatic microsomal enzyme system.
7. Multivitamin.
8. If indicated: antibiotics, digoxin, NG-tube, etc.

SPECIFIC MEASURES OF THYROID STORM

On the basis of clinical experiences, Formula TS or TC 41668-24-6 (Tjokropawiro 2005) has been routinely used in Surabaya, and the essential drugs should be given in a sequent number of such a Formula as follow: PTU: 4, One hour interval: 1, Lugol's Solution or SSKI: 6, Propranolol: 6, Hydrocortisone: 8, Clinical Improvement (hour): 24, and Resolve the crisis (day): 6. The Formula TS or TC 41668-24-6, the revision of Formula 41668 (Tjokropawiro 2002) is a practical guideline of the specific measures of TS and can be used as a target of clinical outcomes of adequate therapy.

The description of this Formula can be followed bellow. "4" means: 400 mg loading dose of PTU, with maintenance of PTU 100-200 mg every 4 hours. PTU is given to inhibit synthesis of TH by preventing organification and trapping of iodide to iodine and by inhibiting coupling of iodotyrosines; also inhibits peripheral conversion of T4 to T3, an important component of management. Methimazole: inhibits synthesis of TH by preventing organification of iodide to iodine and coupling of iodotyrosines. Although at least 10 times more potent than PTU on a weight basis, it does not inhibit peripheral conversion of T4 to T3. Initial dose; 40 mg per oral, with maintenance dose: 10 mg every 4 hours. "1" means: minimally 1 hour after initiation of PTU, iodides may be started.

Table 3. Diagnostic Criteria for Thyroid Storm
(Burch and Wartofsky, 1993, Summarized: 2005)

Thermoregulatory Dysfunction			Cardiovascular Dysfunction		
Temperature			1). Tachycardia		
	37.2-37.7 °C	5		99-109	5
	37.8-38.3 °C	10		110-119	10
	38.4-38.8 °C	15		120-129	15
	38.9-39.4 °C	20		130-139	20
	39.5-39.9 °C	25		≥140	25
	≥ 40 °C	30	2). Congestive Heart failure		
Central Nervous System Effects			* Absent		
* Absent		0	* Mild		
* Mild		10	- Pedal edema		
- Agitation			* Moderate		
* Moderate		20	- Bibasilar rales		
- Delirium			* Severe		
- Psychosis			- Pulmonary edema		
- Extreme lethargy			3). Atrial fibrillation		
* Severe		30	* Absent		
- Seizure			* Present		
- Coma					
Gastrointestinal-Hepatic Dysfunction			Precipitant History		
* Absent		0	* Negative		
* Moderate		10	* Positive		
- Diarrhea					
- Nausea/vomiting					
- Abdominal pain					
* Severe		20			
- Unexplained jaundice					

A score of 45 or greater is highly suggestive of thyroid storm

A score of 25-44 is suggestive of impending thyroid storm

A score below 25 is unlikely to represent thyroid storm.

The first "6" means: 6 drops every 6 hours of Lugol's solution or SSKI can be started 1 hour after PTU, and should be evaluated after 6 days. Iodides inhibit the release of TH from the thyroid gland. Precede iodide administration with thionamides to prevent increased intrathyroidal hormone stores. Lithium carbonate also can be used if patients are hypersensitive to iodine.

The second "6" means: every 6 hours, 10-40 mg propranolol orally should be given to decrease heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Reevaluation should be done after 6 day administration of propranolol. Or 0.5-1 mg intravenously every 3 hours, monitoring its effects of cardiac rate. Beta blocker is mainstay therapy to control autonomic effects of TH. It also blocks peripheral conversion of T₄ to T₃. Esmolol, a short-acting selective beta 1-antagonist, has been used successfully in children, as has labetalol in adults. Propranolol is often the only adjunctive drug necessary to control thyroid storm.

"8" means: 100-200 mg intravenous injection of hydrocortisone hemisuccinate every 8 hours to block the conversion of T₄ to T₃. Used of steroids has been associated with improved survival. Stress doses are required to replace accelerated production and degradation of cortisol induced by TH. If steroids are not administered, acute glucocorticoid deficiency theoretically might occur because demand may outpace production. Steroid may suppress immune function, but benefit outweighs risk in serious conditions such as thyroid storm. "24" means: with such a regimen, clinical improvement should be achieved within 24 hours.

The last "6" means: adequate therapy with such a regimen should resolve the crisis within 6 days. The precipitant of the thyroid storm is often the cause of death. If indicated, cholestyramine or colestipol can be given 20-30 g/day (Greenspan et al. 2004).

REFERENCES

- Belchetz, P, Hammond, PJ 2003, 'Thyroid', in *Mosby's Color Atlas and Text of Diabetes and Endocrinology 1*, p. 169.
- Burch, HB & Wartofsky, L 1993, 'Life-threatening thyrotoxicosis: Thyroid Storm', *Endocrinol Metab Clin North Amer*, vol. 22, p. 263.
- Colebunders, R, Bordoux, P & Bekaert, J et al. 1984, 'Determination of free thyroid hormones and their binding proteins in a patients with severe hyperthyroidism (thyroid storm?) and thyroid encephalopathy', *J Endocrinol Invest*, vol. 7, p. 379.
- Ghobrial, MW & Ruby, EB 2002, 'Come and thyroid storm in apathetic thyrotoxicosis', *South Med J*, vol. 95, no. 5, p. 552.
- Greenspan, FS & Gardner DG, 2004, 'Endocrine emergencies', *Basic & Clinical Endocrinology*, vol. 7, p. 867.
- Hall, JB, Schmidt, GA, Wood, LDH 1999, 'Thyroid disease', *Principles of Critical Care*, vol. 2, p. 715.
- Hughes, SCA, David, LA, Turner, R 2003, 'Storm in a T-CUP: thyroid crisis following trauma injury', *Int J Care Injured*, vol. 34, p. 946.
- Singhal, A & Campbell, D 2003, *Thyroid Storm*. Retrieved from www.emedicine.com/ped/topic2247.htm
- Tietgens, S & Leinung, MC 1995, 'Thyroid storm', *Med Clin of N Amer*, vol. 99, p. 169.
- Tjokroprawiro, A 2002, *Practical Guidelines with Formula 41668 for the Treatment of Thyroid Crisis*, Clinical Experiences: Morning Report Dept. of Internal Medicine, Airlangga University School of Medicine, Surabaya 4 February.
- Tjokroprawiro, A 2005, *Revised Practical Guidelines with Formula 41668 for the Treatment of Thyroid Crisis*, Clinical Experiences: Morning Report Dept. of Internal Medicine, Airlangga University School of Medicine, Surabaya 4 February.
- Turner, HE & Wass, JAH 2003, 'Thyroid crisis' in *Oxford Handbook of Endocrine and Diabetes 1*, p. 35.