

SYSTEMATIC REVIEW ARTICLE

Management of Cardiogenic Shock due to Thyrotoxicosis: A Systematic Literature Review

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Abstract: Background: A grave complication of thyrotoxicosis, or thyroid storm, is the development of heart failure and cardiomyopathy. Recognizing this condition is imperative in preventing further left ventricular dysfunction and cardiogenic shock. This manuscript aims to review the literature on cardiogenic shock associated with thyrotoxicosis and present management recommendations on this rare condition.

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Methods: A literature search was performed in December of 2018, using the PubMed medical search engine. A systematic search was carried out using the keywords *Thyroid Storm AND Cardiogenic Shock* and *Thyrotoxicosis AND Shock*.

Management: Decrease of thyroid hormone levels using therapeutic plasma exchange LV Unloading and ventilation by Impella and Extracorporeal Mechanical Ventilation (ECMO).

Conclusion: Patients presenting with thyroid storm-induced shock may not be suitable candidates for traditional management with β -adrenergic blockers (β -blockers). The use of β -blockers could exacerbate their condition. Through extensive literature review on this rare condition, the most effective management was found to be therapeutic plasma exchange in order to decrease thyroid hormone levels, which have direct toxic effect on the heart. Furthermore, the use of ECMO and Impella is advised to reduce pressure on the heart and ensure the patient's organs are well oxygenated and perfused while the left ventricle is recovering.

Keywords: Thyrotoxicosis, cardiogenic shock, shock, thyroid storm, ECMO, impella, therapeutic plasma exchange.

1. INTRODUCTION

1.1. Rationale

A grave complication of thyrotoxicosis or thyroid storm is the development of heart failure and cardiomyopathy. Recognizing this condition is imperative in preventing further left ventricular dysfunction and cardiogenic shock. As noted in the literature, this condition is exceptionally rare; only six percent of patients develop heart failure and cardiomyopathy as a result of thyrotoxicosis with an even smaller percentage having left ventricular dysfunction [1]. Although the incidence rate for this condition is low, the mortality rate is close to thirty percent because of the association between cardiogenic shock and hypotension [2].

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1.2. Objectives

This manuscript aims to review the literature on cardiogenic shock associated with thyrotoxicosis and present management recommendations on this rare condition.

2. METHODS

2.1. Protocol and Registration

This manuscript's protocol was not sent for review. For the purpose of this manuscript, *Prisma* guidelines were followed.

2.2. Eligibility Criteria

After the use of keywords, exclusion criteria were applied to the findings. These included papers focused on right heart failure and heart failure but no cardiogenic shock, pregnancy, Iodine or Amiodarone-induced thyrotoxicosis.

The also included review articles on thyrotoxicosis and heart failure, and papers in languages other than English (*as shown in Flow Chart*). The choice of having these exclusions was to simply remove any possible etiology for cardiogenic shock other than thyrotoxicosis.

Using the search Key Words ^a	
Yes	No → Excluded
Showing Evidence of Cardiogenic Shock	
Yes	No → Excluded
Other Exclusion factors ^b	
No	Yes → Excluded
Will Use in The Study	

Flow Chart. Showing the method for choosing articles. Table 1 shows the keywords used in PubMed Central. ^aOther exclusions are mentioned in *Eligibility Criteria*. ^b

2.3. Information Sources/Search

A literature search was performed in December of 2018 using the PubMed medical search engine [3].

2.4. Study Selection

A systematic search was carried out using keyword combinations that are mentioned in Table 1. A total of 123 articles were identified with the oldest dating back to 1974 and the most recent being published in 2018.

2.5. Date Collection Process

Three researchers reviewed these articles independently and applied the exclusion criteria.

2.6. Data Items

Reviewers as well as the rest of the team used no funding for collection of data, analysis and providing the manuscript.

2.7. Risk of Bias in Individual Studies

Risk of bias at individual level for studies is extremely low. As mentioned in the introduction, this is a very rare condition and as a result, all studies were case reports, merely reporting patient management rather than structured studies.

2.8. Summary Measures

Principal summary is based on the method of management and the outcome (live/death) as well as average hospital length of stay.

2.9. Synthesis of Results

Descriptive analysis, such as mean or median and percentage, was performed for continuous variable proportions. For categorical patient variables, frequencies were used. Comparisons were made using Kaplan Meir estimator which was used for survival analysis. A p level of <0.05 was used to determine statistical significance. Prism software 8.0 was used for calculations.

2.10. Risk of Bias Across Studies

The only bias identified across studies is at the level of the provider who executed management. This is based on their level of knowledge on the subject matter and their preferred methods.

3. RESULTS

A total of twelve articles, shown in Table 2, were found after applying the exclusion criteria. The majority of articles were case reports due to the rarity of the condition. Data on age, sex, ejection fraction, the methodology of treatment (use of β-blocker, ECMO, Impella, or TPE) were extracted from all of the articles as presented in Table 3. All patients presented here had cardiogenic shock. Some presented with hemodynamic instability and some developed cardiogenic shock shortly after use of β-blockers. One patient from the fourth article cited was excluded since the patient was managed for congestive heart failure by the use of diuretics and was later found to have thyrotoxic-induced cardiogenic shock.

Table 1. Search Key Words and results.

Number	Search	Result
1	Thyrotoxicosis/Thyroid Storm + Cardiogenic Shock	13
2	Thyrotoxicosis/Thyroid Storm + Cardiogenic Shock + ECMO	2 ^t
3	Thyrotoxicosis/Thyroid Storm + Cardiogenic Shock + Impella	0
4	Thyrotoxicosis/Thyroid Storm + Cardiogenic Shock + Plasmapheresis	0
5	Thyrotoxicosis/Thyroid Storm + Pulmonary Edema + Heart Failure	16
6	Thyrotoxicosis/Thyroid Storm + ECMO	9
7	Thyrotoxicosis/Thyroid Storm + Impella	0
8	Thyrotoxicosis/Thyroid Storm + Plasmapheresis	85

Note: t: repeat articles.

Table 2. Articles that met criteria for use in this review paper.

Number	Author	Year of Publication
1	Abubakr <i>et al.</i> [10]	2017
2	Eyadiel <i>et al.</i> [9]	2018
3	Allencherril <i>et al.</i> [24]	2015
4	NGO <i>et al.</i> [7]	2007
5	Kim <i>et al.</i> [6]	2018
6	Dahl <i>et al.</i> [1]	2008
7	Chao <i>et al.</i> [25]	2015
8	Kiriyama <i>et al.</i> [34]	2017
9	White <i>et al.</i> [32]	2018
10	Koball <i>et al.</i> [35]	2010
11	Hsu <i>et al.</i> [36]	2011
12	Palkar <i>et al.</i> [37]	2012

A descriptive analysis of the data is shown in Table 4. A total of 20 patients were identified in 12 case reports. These patients were divided into two groups based on the medical management they received. The case group was categorized by the use of mechanical support (ECMO and/or Impella), and the control group comprised of patients who were administered medical therapy (β -blocker and inotropes) only. Propranolol was the β -blocker used in all papers that used β B, except for the case presented by Eyadiel *et al.* Days of de-cannulation from ECMO are included in Table 3 in order to find if the use of TPE shortened the time to de-cannulation from ECMO. Left ventricular ejection fraction of patients was divided into four groups (a: <10%, b: 10-20%, c: 21-30%, d: >30%) as shown in Table 4.

Statistical analysis was performed for survival study. Length of hospital stay was used as survival days since the diagnosis of the condition. For Mechanical Support group, in patients with no HLS documented, days to de-cannulation from ECMO were used instead. In the medical therapy group, two patients had no HLS and therefore were removed from analysis. As demonstrated in Survival Graph (Fig. 1), survival rate difference was not statistically significant between the groups with P-value of 0.68. Mean days to de-cannulation from ECMO were calculated for live patients and were found to be 6.5 days.

4. DISCUSSION

4.1. Presentation and Pathophysiology

The direct and indirect actions of T_3 are contributing to the main effects of thyrotoxicosis on the heart and cardiovascular system. Heart rate and left ventricular contractility increase as a result of hyperthyroidism while systemic vascular resistance decreases [1]. The decrease in vascular resistance will lead to a decrease in renal perfusion, which in turn activates the *renin-angiotensin-aldosterone* system. This will

lead to an increased preload and as a result, increased cardiac output [4]. All of these changes lead to decreased myocardial contractile reserve, predisposing the patient to heart failure [1, 4]. This progression can be seen in patients with no prior cardiac injury.

Anywhere from 10-25% of patients with hyperthyroidism are known to have atrial fibrillation (AF) [4]. From the reviewed literature, AF along with rapid ventricular response (RVR) is one of the main electrical abnormalities observed in the patients with thyrotoxicosis at the time of presentation (TSH <0.5 mU/L or non-detectable) [5-8]. Tachycardia is a known leading factor of heart failure in these patients due to their low myocardial contractile reserve [4].

4.2. Management

β -adrenergic blockers, along with anti-thyroid hormone medications, are traditionally used as first-line management for patients presenting with thyrotoxicosis [1, 4]. Propranolol is a prominent medication utilized for thyrotoxicosis management since it decreases the conversion of T_4 to the more active T_3 form. However, development of cardiogenic shock after administration of β -blockers was found in many of the articles reviewed [5, 6, 9, 10]. Abubakr *et al.* pointed to the fact that in a hyperthyroid state, with the patient experiencing high cardiac output, β -blockers will not place the patient at risk of hemodynamic instability [9]. Patients that have decreased left ventricular ejection fraction (LVEF), propranolol is not recommended due to its risk of cardiogenic shock; this, in turn, would mandate the use of volume resuscitation and pressors drugs. Ikram *et al.* invasively monitored hyperthyroid and cardiac failure patients and were able to demonstrate that decreased cardiac response with the use of β -adrenergic blocker was due to decreased stroke volume and increased pulmonary artery diastolic pressure [11]. This was observed in all cases of cardiogenic shock chosen in our literature review.

Table 3. Descriptive analysis of papers reviewed. EF is Ejection Fraction of Left Ventricle at time of presentation. U/S is result of ultrasound showing either Left Ventricular failure (LVF) or Right Ventricular Failure (RVF). BB is if β -blocker was used or not. HLS is hospital length of stay in days. Outcome is if patient stayed alive or expired. A fib/Flutter is presence of these abnormal rhythms on admission.

Author	Year	Age	Sex	A-Fib/Flutter	EF	U/S	BB	Pressor	ECMO	IMPELA	TPE	ECMO De-cannulation	HLS	Outcome
Abubakr <i>et al.</i>	2017	39	M	Yes	15-20%	LVF	Y	Y	N	N	Y	-	11	Expired
Eyadiel <i>et al.</i>	2018	27	F	No	<10%	LVF	Y	Y	Y	Y	Y	6 d	-	Live
Allencheril <i>et al.</i>	2015	29	M	Yes	<20%	LVF	Y	Y	Y	N	N	7 d	-	Live
NGO <i>et al.</i>	2007	32	M	Yes	25%	LVF	Y	Y	N	N	N	-	9	Live
		28	M	Yes	20%	LVF	Y	Y	N	N	N	-	9	Expired
Kim <i>et al.</i>	2018	52	M	Yes	<20%	LVF	Y	Y	Y	N	N	6 d	14	Live
Dahl <i>et al.</i>	2008	32	F	No	-	-	Y	-	N	N	N	-	-	Live
Chao <i>et al.</i>	2015	47	M	-	24% (20-24)	LVF	N	Y	Y	N	N	3.4 d	-	Expired
		43	M	-										Expired
		37	F	-										Live
		42	M	-										Live
		33	F	-										Live
Kiriyama <i>et al.</i>	2017	54	F	Yes	<20%	LVF	N	N	Y	N	N	18 d	18	Live
White <i>et al.</i>	2018	57	F	Yes	<10%	LVF	N	Y	Y	N	N	10 d	53	Live
Koball <i>et al.</i>	2010	68	F	-	-	-	Y	Y	N	N	Y	-	18	Live
Hsu <i>et al.</i>	2011	47	M	Yes	32%	LVF	N	Y	Y	N	N	-	5	Expired
		43	M	No	20%							5 d	20	Live
		37	F	Yes	32%							5 d	5	Live
		42	M	No	29%							5 d	5	Live
Palkar <i>et al.</i>	2012	27	F	No	40%	LVF	Y	-	N	N	N	-	-	Live

For this reason, β -blockers should be prescribed with caution. Several articles recommend using ultra-short-acting variants (*i.e.* esmolol with a 9-minute half-life) [12, 13]. The rationale is that if there is evidence of decreased myocardial function, like worsening congestive heart failure or cardiogenic shock, the ultra-short-acting β -blockers can be discontinued and the effects reversed. Additionally if propranolol is used, a low intravenous dose (*i.e.* 0.5 mg) should be administered first. Choudhury & MacDermot mentioned if cardiac failure in a thyrotoxicosis patient is found to be truly secondary to congestion (decompensating due to an increase in

intravascular volume), negative inotropic β -blockers should be avoided in patients with underlying ischemic, hypertensive, or valvular heart disease [14].

A study published by Mohananeey *et al.* examined the Nationwide Inpatient Sample and found the rate of cardiogenic shock in patients who present with thyroid storm to have increased from 0.5% in 2003 to 3% in 2011. [15] They further revealed a 40% decrease in mortality for this patient population. The researchers attributed the decreased mortality rate to the increased use of intra-aortic balloon pump

Table 4. Descriptive analysis of patients in the two groups of ECMO and/or Impella vs. beta-blocker (BB) and/or therapeutic plasma exchange (TPE). For age mean is presented. For sex, percentage of male is presented. For ejection fraction (EF), results were divided into four categories and the number of patients in each sub category is presented as a percentage. Group a: EF <10%, b: 10-20%, c: 21-30%, d: >30%.

-	Mechanical Support (N=14)	Medical Therapy (N=6)
Age (yo)	42	38
Sex (Male)	57%	67%
Ejection Fraction	a: 14.3%	a: 0%
-	b: 28.6%	b: 50%
-	c: 42.9%	c: 25%
-	d: 14.3%	d: 25%

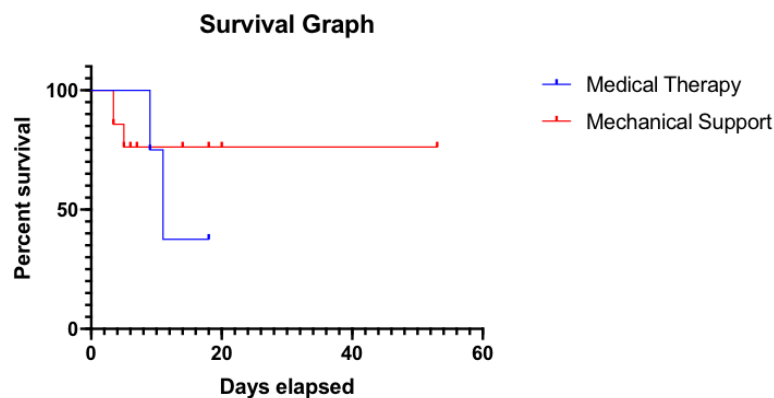


Fig. (1). Survival graph. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

(IABP) and extracorporeal mechanical ventilation (ECMO) for the patients in intensive care unit.

4.3. Management of Cardiogenic Shock in Thyrotoxicosis

4.3.1. Decrease of Thyroid Hormone Levels Using Therapeutic Plasma Exchange

Use of anti-thyroid medications has shown to improve cardiac function, but this result could take weeks to observe [4]. For recovery of cardiac function, radioactive iodine ablation or thyroidectomy have been shown to be effective in the past [16, 17]. However, in light of cardiogenic shock and hemodynamic instability, these methods are not feasible. Use of therapeutic plasma exchange (TPE) for management of thyrotoxicosis has been documented since 1974 [18]. A recent publication by Eyadiel *et al.* demonstrated the use of therapeutic plasma exchange to decrease the thyroid hormone levels in a patient with cardiogenic shock secondary to thyrotoxicosis [8]. It has been well documented that in patients with acute thyrotoxicosis, therapeutic plasma exchange can remove thyroid hormones as well as thyroid gland autoantibodies, catecholamines and cytokines [19, 20, 30, 36]. In research by Subahi *et al.*, a four-step algorithm was created for the management of thyrotoxic crisis [21]. Early use of plasma exchange was one of the proposals made in their algorithm for clearing the thyroid hormone. Another area where therapeutic plasma exchange (TPE) might be

used is prior to urgent surgery. In a retrospective study, Ezer *et al.* demonstrated the successful use of TPE in patients with thyrotoxicosis not responding to classic medical therapy and in need of urgent surgery [22]. These surgeries were either on the thyroid or urgent orthopedic surgeries, and all patients experienced outstanding results with fresh frozen plasma and albumin exchange transfusion. The same results were noted by Simsir *et al.* who confirmed the effectiveness of TPE as an alternative to anti-thyroid medications, especially in patients who experience adverse effects or are being prepared for urgent surgery [19]. Our study found an average of 6.5 days to de-cannulation from ECMO. Eyadiel *et al.* demonstrated that the use of TPE along with mechanical support was shown to decrease de-cannulation time from ECMO in their report [8]. More studies are needed to prove a shortened time to de-cannulation from mechanical support with the use of TPE.

4.3.2. LV Unloading by Extracorporeal Mechanical Ventilation (ECMO) and Impella or IABP

Mohananey *et al.* showed a 40% improvement in survival with mechanical support [15]. Maintaining blood oxygenation is of great importance in patients with cardiogenic shock. This task was performed by the use of ECMO in the reviewed articles [5, 8, 15, 23-24] ECMO is a temporary measure used in order to replace the function of the heart and/or lungs. This, in turn, allows time for organ recovery.

ECMO has been shown to be useful in conditions like respiratory distress syndrome, acute myocardial infarction, post cardiomyopathy shock, and severe cardiomyopathy [25-29].

The patients mentioned in the reviewed articles had compromised cardiac contraction and hypotension despite the use of pressers. Schrage *et al.* have shown the successful use of venoarterial ECMO in patients who present with cardiogenic shock [30]. White *et al.* performed a systematic review in which there were a 78.5% survival rate and near complete recovery of left ventricular function; these patients were managed with VA-ECMO [31]. The main drawback observed by the researchers was elevated afterload on the left ventricle. This can be overcome by use of Impella, as used by Eyadiel *et al.* [8] In a retrospective study performed by Colombier *et al.*, it was observed that the utilization of Impella was incredibly beneficial in patients presenting with refractory cardiogenic shock and were not responding well to the simultaneous use of VA-ECMO and intra-aortic balloon pump [32]. There was a higher 30-day survival rate in these patients. Implementing Impella would take pressure off of the left ventricle and provide time for recovery.

In several of the studies reviewed, IABP was another device used to supplement ECMO; these devices are known to increase myocardial oxygen perfusion and indirectly increase cardiac output by decreasing the afterload of the heart [23-24, 33, 35].

CONCLUSION

The most important factor in patients presenting with thyroid storm-induced shock is to determine if left ventricular ejection fraction is affected. These patients might not be candidates for traditional management with β -adrenergic blockers. Use of β -blockers could worsen their condition by causing hemodynamic instability and necessitating inotropes. By reviewing the literature on this rare condition, the most effective management was found to be therapeutic plasma exchange which decreased thyroid hormone levels and have direct toxic effect on the heart. Further use of mechanical support (ECMO and Impella) is advised to take pressure away from the heart and ensures that patient's organs are well oxygenated and perfused while the left ventricle is recovering.

This quasi-meta analysis failed to attain statistical significance in length of survival between the mechanical support and medical therapy groups. Statistical difference in our study could be attributed to several factors including the low number of studies reviewed due to the rarity of the case; this small sample size leads to low power. One should keep in mind when researching the topic that not many articles are written on negative results, especially in cases of mortality.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING:

PRISMA guidelines and methodologies were followed.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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