ISSN 2664-3987 (Print) & ISSN 2664-6722 (Online)
South Asian Research Journal of Medical Sciences
Abbreviated Key Title: South Asian Res J Med Sci

| Volume-5 | Issue-4 | Jul-Aug -2023 | **DOI: 10.36346/sarjms.2023.v05i04.003**

Original Research Article

Use of Plasmapheresis in the Treatment of Thyrotoxicosis Secondary to Graves' Disease at the National Medical Center 20 de Noviembre ISSSTE: Case Report

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Article History
Received: 20.05.2023
Accepted: 27.06.2023
Published: 09.07.2023

Abstract: Thyrotoxicosis refers to the clinical syndrome secondary to excess of circulating thyroid hormones, thyroid storm is an extreme manifestation of thyrotoxicosis, and which can reach 10-30% mortality with treatment depending on the series. This rare but serious complication occurs mainly in patients with Graves' disease (GD) who account for 60% to 80% of cases of hyperthyroidism. Both plasmapheresis/therapeutic plasma exchange (TPE*)* and emergency surgery have been used to treat thyroid storm in patients who respond poorly to first-line therapeutic measures. We present the case report of three patients with severe disease (GD) managed at the National Medical Center 20 de Noviembre ISSSTE using TPE as a bridge treatment to thyroidectomy, of which the indication for two patients was intolerance to antithyroid drugs and one with intolerance to antithyroid drugs in addition to impending thyroid storm. Between 4-5 sessions of TPE were performed in which there was a decrease in T4L and anti-TSH receptor antibodies (TSH-R-Ab), in addition to significant clinical improvement, which allowed us to perform thyroidectomy safely. Therefore, we consider that TPE is a fast, safe, and effective bridge treatment to surgery, which should be considered in patients with no response or intolerance to thionamide treatment, in centers where TPE and immediate surgery are available.

Keywords: Plasmapheresis, Thyrotoxicosis, Thyroidectomy, Graves' Disease, a case report.

1. INTRODUCTION

Thyrotoxicosis refers to the clinical syndrome secondary to excess of circulating thyroid hormones. Thyroid storm is an extreme manifestation of thyrotoxicosis and can reach 10-30% mortality with treatment depending on the series [1]. This rare but serious complication occurs mainly in patients with Graves' disease (GD) who account for 60% to 80% of cases of hyperthyroidism [2].

GD is caused by autoantibodies that mimic the action of thyroid stimulating hormone (TSH) by binding to and activating the TSH receptor (TSH-R). As with most autoimmune disorders, a combination of many different genetic and environmental factors may contribute to the etiology [3]. GD hyperthyroidism is treated by reducing thyroid hormone synthesis with antithyroid drugs (ATD) or thionamides as first line or by reducing the amount of thyroid tissue with treatment with radioiodine ablation therapy (RAI) or total thyroidectomy in unresponsive cases [3].

Both plasmapheresis (TPE) and emergency surgery have been used to treat thyroid storm in patients who respond poorly to first-line therapeutic measures. TPE is a therapeutic procedure in which the patient's blood is passed through a medical device that separates the plasma from other blood components. The plasma is removed and replaced

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with a replacement solution, such as a colloid solution (e.g., albumin and/or plasma) or a crystalloid/colloid solution combination [4]. In a review of the literature there are case reports, where TPE significantly decreased free T4 and T3, and total T3 and T4 levels (Garla, 2018) and allowed control of thyrotoxicosis and a bridge to the performance of definitive treatment (thyroidectomy) [5].

The following describes the experience of the use of plasmapheresis (TPE) as a bridge therapy for the performance of definitive treatment (thyroidectomy), in three patients with severe thyrotoxicosis due to severe disease at the Centro médico nacional 20 de Noviembre, a third level of care center. "This case report was prepared following CARE Guidelines" [7].

2. PATIENTS AND METHODS

Patient 1

45-year-old male, mixed race, smoking for 10 years (smoking rate of 0.5 packs/year) and no comorbidities. He starts with weight loss, tachycardia and anxiety is diagnosed with Graves' disease (GD) without Graves' orbitopathy (GO) in June 2019.

Patient 2

31-year-old female, mixed race, smoking since age 12 (smoking rate of 1.75 packs/year), denied allergies, history of asthma. She starts in puerperium with weight loss, distal tremor, inability to breastfeed, and goiter is diagnosed with GD in the past 2 years ago (September 2016) and GO is added (CAS 4/7).

Patient 3

35-year-old woman, mixed race, smoking for 19 years, iodinated contrast allergy and history of contact dermatitis. She starts 2 years ago (2020) with tremor, palpitations, tachycardia and weight loss is diagnosed with GD without GO.

Table 1 summarizes the demographic characteristics of the patients reported.

Table 1: Characteristics of patients with Graves' disease undergoing plasmapheresis

	Patient 1	**Patient 2**	**Patient 3**
Gender	Male	Female	Female
Age (years)	35	31	35
Time of evolution (years)	6 month	2	2
Allergies	no	thiamazole	Iodinated contrast agents
Smoking	smoking rate of 0.5 packs/years	smoking rate of 1.75 packs/years	positive
Comorbidities	-	asthma	contact dermatitis
Graves' orbitopathy	no	sí	no

2.1. Previous therapy

Patient 1 was started on thionamides (ATD), beta-blocker and anxiolytic; during follow-up the dose of ATD was increased without reaching control of thyroid function tests (TFT), at 3 months he presented icteric syndrome with alterations in liver function tests and was hospitalized; during hospitalization with cholestasis, ERCP and cholecystectomy were performed, in addition to liver biopsy where cholestasis was reported, probably secondary to drugs. She presented imminent thyroid storm (Burch Wartofsky of 25 points), plasmapheresis was indicated as urgent treatment for total thyroidectomy, 4 sessions of plasmapheresis were performed with follow-up with TFT and anti-TSH receptor antibodies (see Table 2), and biochemical control was achieved, and she underwent thyroidectomy without complications. Patient is currently on levothyroxine, calcium and vitamin D replacement.

In patient 2, ATD was indicated, and she presented urticaria, the dose is unknown, so management with beta-blocker is started, which exacerbates asthma and causes poor adherence to treatment. During follow-up due to persistent thyrotoxicosis, comorbidities and because the patient expressed the desire to become pregnant, it was decided to perform plasmapheresis as a bridge treatment for total thyroidectomy, 5 sessions of plasmapheresis were performed with TFT and TSH-R-Ab for follow-up (see table 2), and biochemical control was achieved, she underwent thyroidectomy without complications during surgery; currently in substitution with levothyroxine, calcium orally.

ATD is started in patient 3 who with a maximum dose of 90 mg/day presents intense pruritus, iodine lugol is added and an allergic reaction is documented; she is sent to our center for definitive treatment. Due to persistent

thyrotoxicosis, plasmapheresis was indicated (5 sessions) with TFT and antibodies during follow-up (see table 2), euthyroidism was achieved and she underwent total thyroidectomy without complications during the procedure; currently with levothyroxine substitution.

2.2. Laboratory tests

All three patients had preoperative TFT showing suppressed TSH, elevated T4L (3-4 times ULN) and elevated TSH-R-Ab in patients 2 and 3 (see Table 2). Patient 1 with abnormal liver function tests with cholestatic pattern unlike the rest. TFT and TSH-R-Ab were performed prior to each plasmapheresis session, taking normalization of T4L as a criterion for euthyroidism.

Table 2: Baseline characteristics of thyroid profile and antibodies prior to thyroidectomy

	Patient 1	**Patient 2**	**Patient 3**
TSH (mUI/L) (0.4-5.1)	0.004	0.017	0.029
T4T (ug/dl) (4.5-12.5)	16.9	24	17.6
T4L (ng/dl) (0.89-1.76)	>6.00	> 6.00	4.80
T3T (ng/dl) (84-172)	519	>600	345
T3L (pg/ml) (2.4-5.6)	13.8	28.8	9.59
TSH-R-Ab (UI/L) (< 1.75)	13.6	37.5	13.6

2.3. Chronogram

Each patient was seen jointly by the endocrinology, general surgery and blood bank services for indication and coordination of TPE and total thyroidectomy when euthyroidism was reached. Prior written informed consent was obtained from all patients for Mahurkar catheter placement and TPE. ATD was discontinued prior to starting TPE. Plasmapheresis was performed consecutively daily and thyroid profiles were taken before each session, and their requirement was guided by the decrease in T4L and clinical manifestations of each patient; when euthyroidism was reached, total thyroidectomy was performed (see Table 3).

Table 3: Plasmapheresis session schedule

Patient 1 (#session)	**T4L (ng/dl) (0.89-1.76)**	**TSH-R-Ab (UI/L) (< 1.75)**	**Patient 2 (#session)**	**T4L (ng/dl) (0.89-1.76)**	**TSH-R-Ab (UI/L) (< 1.75)**	**Patient 3 (#session)**	**T4L (ng/dl) (0.89-1.76)**	**TSH-R-Ab (UI/L) (< 1.75)**
PrePLEX	>6.00	13.6		>6.00			4.8	13.6
1	4.62		1	6.00		1	3.81	3.89
2	6.0		2	5.66	37.5	2	3.17	1.96
3	3.71	3.1	3	3.07	35.5	3	2.31	1.80
4	2.02		4	2.72	31.9	4	2.15	< 0.8
	1.44		5	2.83		5	1.9	< 0.08
Post-surgery				2.4	36.2			

3. RESULTS

All patients manifested significant improvement of clinical symptoms after TPE (see Table 4). There was decrease in baseline T4L of 43.7%, 47.1% and 39.5% in patients 1, 2 and 3 respectively at the last TPE prior to surgery (see Figure 1). Patient 1 required 4 sessions of TPE compared to 5 sessions of TPE for patients 2 and 3. Basal TSH-R-Ab decreased 77.2%, 15%, 99.5% in patients 1, 2 and 3 respectively (see Figure 2).

Table 4: Biochemical comparison of thyroid profile and antibodies before and after the last plasmapheresis session

	Patient 1		**Patient 2**		**Patient 3**	
	Pre	Post	Pre	Post	Pre	Post
TSH (mUI/L) (0.4-5.1)	0.004	0.036	0.100	0.043	0.029	0.031
T4T (ug/dl) (4.5-12.5)	15.6	5.47	17	9.94	17.6	4.02
T4L (ng/dl) (0.89-1.76)	4.62	2.02	> 6.00	2.83	4.80	1.90
T3T (ng/dl) (84-172)	549	66.5	452	193	345	111
T3L (pg/ml) (2.4-5.6)	13.2	4.78	14	7.22	9.59	2.83
TSH-R-Ab (UI/L) (< 1.75)	13.6-	3.1	37.5	31.9	13.6	<0.08
Number of plasmapheresis	4		5		5	

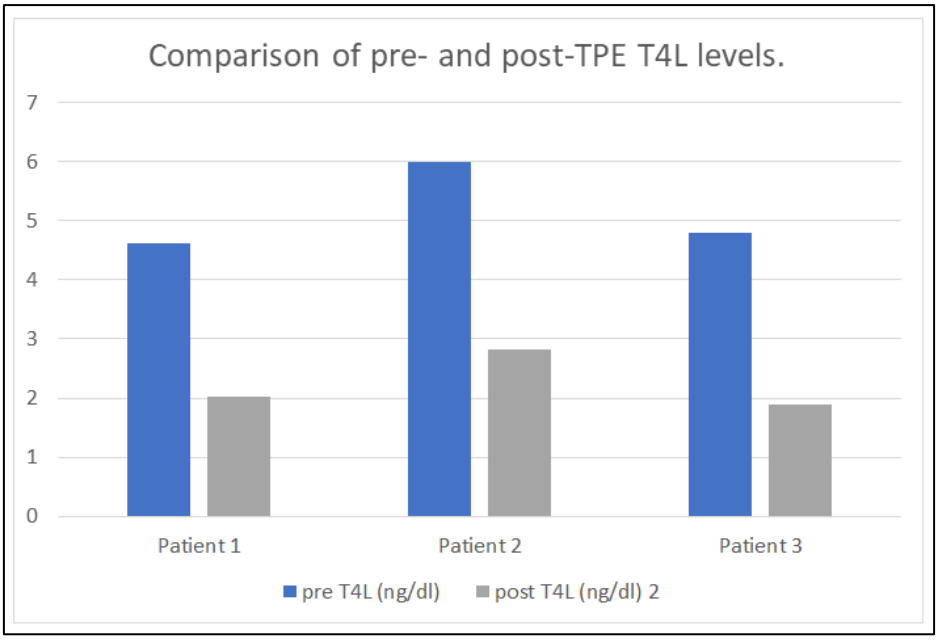

Figure 1: Comparison of pre- and post-TPE T4L levels

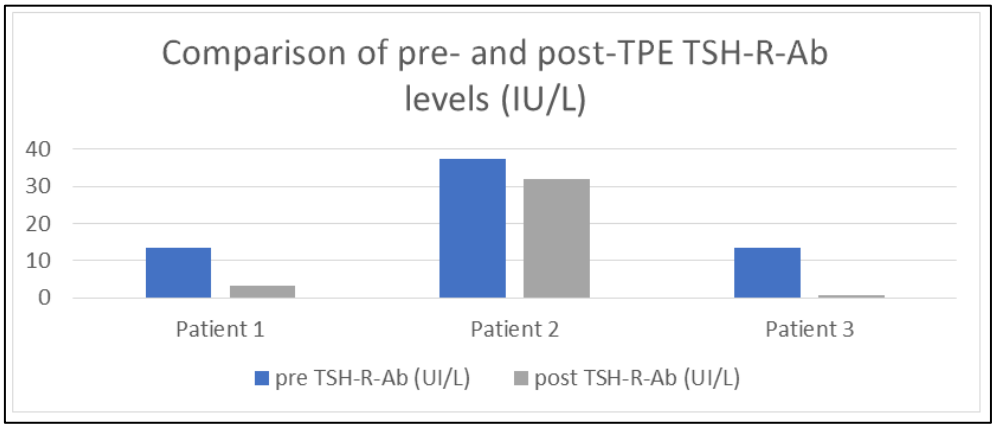

Figure 2: Comparison of pre- and post-TPE TSH-R-Ab levels (IU/L)

4. DISCUSSION

We can observe in the three patients decrease of T4L and clinical improvement; TSH remained without significant changes despite the normalization of thyroid hormones, probably due to the negative feedback time of thyroid hormones on the hypothalamic-pituitary-thyroid axis, this phenomenon has been related to the presence of still high serum concentrations of stimulating TSH-R-Ab, which through binding to TSH receptors in the follicle-stellate cells of the pituitary down-regulate the release of TSH [2]. Regarding the TSH-R-Ab all presented a decrease of more than 50%, except in patient 2 with diagnosis of GO (CAS 4/7), also with values > 12 IU/L which are considered a prognosis of relapse at 2 years of 60%. Four to five sessions of TPE were necessary to reach euthyroidism and to be able to perform thyroidectomy with the lowest possible risk of thyroid storm; this number of sessions agrees with the number recommended in the apheresis guide. In the latest edition of the American Society for Apheresis (ASFA) clinical practice guideline on the use of apheresis published in Journal of Clinical Apheresis (JCA) (2019) classifies its use in the context of hyperthyroidism as category II, which states that the role of TPE is accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other thyroid storm treatment modalities and with recommendation grade 2C, which should be continued until clinical improvement is observed; and usually with a duration of 3 to 6 procedures to achieve clinical stabilization [4]. The indication for TPE was mainly intolerance due to adverse effects of ATD; which were urticaria and pruritus in patient 2 and 3 respectively, which are common reactions (1-5%); however, patient 1 presented hepatotoxicity, which is the least frequent (<0.1%), in addition to the fact that the latter was at risk of imminent thyroid storm. Both TPE and emergency surgery have been used to treat thyroid storm in patients who respond poorly to first-line therapeutic measures. TPE is usually performed in patients with thyroid storm with severe symptoms and when the patient does not improve with first-line therapies, or they cannot be used due to toxicity [4]. In rare cases, TPE is used to make the patient with thyrotoxicosis euthyroid before thyroidectomy. The effect of TPE is transient and hormone

levels usually rise again the next day, so total thyroidectomy was coordinated as definitive treatment, without increasing the risk of complications during surgery.

5. CONCLUSIONS

Plasmapheresis is considered a rapid, safe and effective bridge treatment to total thyroidectomy, which should be considered not only in the setting of thyroid storm but also in patients with no response or intolerance to thionamide therapy in centers where TPE and immediate surgery are available.

6. Conflict of Interest

The authors declare that there are no conflicts of interest at the time of publication of this article.

GLOSSARY

ADR: adverse drug reaction.
ASFA: American Society for Apheresis.
ATD: antithyroid drug.
CAS: Clinical activity score.
CMNO: Centro médico nacional 20 de Noviembre.
ERCP: endoscopic retrograde cholangiopancreatography.
GD: Graves' disease.
GO: Graves' orbitopathy.
JCA: Journal of Clinical Apheresis.
RAI: radioiodine ablation therapy.
TFT: thyroid function tests.
TPE: therapeutic plasma exchange.
TSH: thyroid stimulating hormone.
TSH-R: receptor de TSH.
TSH-R-Ab: anti-TSH receptor antibodies.
ULN: upper normal limit.

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