

PREOPERATIVE THERAPEUTIC PLASMA EXCHANGE AND SURGICAL TREATMENT IN THYROTOXICOSIS PATIENTS: A SINGLE-CENTRE RETROSPECTIVE COHORT STUDY

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Abstract

Context. Therapeutic plasma exchange (TPE) provides time for thyroidectomy in thyrotoxic patients.

Objective. TPE is indicated in cases where antithyroid medications cannot be used due to the side effects or attain no adequate hormonal suppression response at the highest dosage and in cases of rapid onset of clinical symptoms. This study presents the treatment results of patients who underwent TPE and were subsequently operated for thyrotoxicosis.

Design. The patients who underwent thyroidectomy and TPE between January 1999 and February 2019 were retrospectively analyzed.

Subjects and Methods. The files of 27 patients with thyrotoxicosis who performed TPE prior to surgery were analyzed in relation to the demographic and clinical features.

Results. We included 15 (55.6%) females, 12 (44.4%) males with a mean age of 44 (23-82) years. The pre-TPE mean free thyroxine (fT4) level was 12 (5-46) pmol/L while free tri-iodothyronine (fT3) level was 34 (17-141) pmol/L. The post-TPE fT4 level was 6 (3-10) pmol/L while the fT3 level was 21 (12-41). There was one case of an allergic reaction during the procedure. In the postoperative follow-up, there was transient hypocalcemia in 8 (29%) patients, permanent hypocalcemia in 1 (3.7%) patient, and surgical site infection in 1 (3.7%) patient.

Conclusion. Preoperative TPE is an alternative treatment option for thyrotoxic patients. This is an especially effective treatment for patients with inadequate response or adverse reaction to antithyroid drugs or patients who need urgent surgery for thyroid storm.

Keywords: Thyrotoxicosis, Therapeutic plasma exchange, Graves' disease, Thyroid storm.

INTRODUCTION

Thyrotoxicosis is a clinical condition characterized by elevated serum thyroid hormone levels and it carries increased morbidity and mortality risks (1-2). The most common cause of thyrotoxicosis is Graves' disease. The second most common cause is iodine deficiency-related toxic multinodular goitre (TMG) and toxic adenoma in iodine sufficient regions. These 3 conditions account for 90-95% of thyrotoxicosis cases (3-4). Elevated thyroid hormone levels cause symptoms such as weight loss despite sufficient feeding, irritation, anxiety, heat intolerance, sweating, palpitations, and muscle weakness.

In treating thyrotoxicosis, alternative treatment options can be used when there is no response to the highest dose of antithyroid drugs or adverse reactions to the antithyroid drugs and in thyroid storm, where symptoms develop rapidly. Therapeutic plasma exchange (TPE) is the forefront alternative treatment in these circumstances because it rapidly clears these hormones, thus lowering the serum hormone levels giving a safe window for definitive treatment (3,5-8). Despite being an invasive procedure with its complications, TPE is an effective treatment option where conventional treatments are inadequate or fail. The disadvantages of TPE are central catheter-specific problems, prolonged hospital stay, catheter site infections, increased risk of bleeding, hypocalcemia, hypotension, transfusion-related complications, pulmonary oedema, and high cost. However, TPE can be safely used preoperatively for patients with thyrotoxicosis or thyroid storm despite the complications. Studies have shown that these complications have low morbidity and mortality rates when managed properly (3,9-11).

This study aimed to share a single-centre

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outcome of the preoperative TPE and subsequent surgery in patients with thyrotoxicosis and/or thyroid storm.

MATERIALS AND METHODS

We performed therapeutic plasma exchange in 27 thyrotoxic patients at the Hematology Apheresis Center between January 1999 and February 2019. All the patients were on follow-up by our Endocrinology and Metabolism Diseases Department. The list of TPE patients was obtained from the register of the hospital's apheresis unit. The indications for TPE were thyrotoxicosis unresponsive to medical treatment, adverse reaction to the treatment and patients that need urgent surgery. The patients who were not subject to thyroidectomy after TPE, the patients with low serum calcium levels preoperatively, patients who were hemodynamically unstable, and patients in which central catheter placement was not performed were excluded from the study. This study has been reported in line with the STROCSS criteria (12).

The demographic characteristics of the patients, the etiology of the thyrotoxicosis, antithyroid drug usage, adverse effects of the medications, pre-treatment liver functions tests levels, haemogram, thyroid hormone, and calcium levels were recorded and analyzed. Also, the solution used for TPE, 5% human albumin or fresh frozen plasma (FFP), the number of TPE sessions, the surgical procedure carried out, histopathology results, surgical complications (RLN injury, haemorrhage, hypocalcemia, and wound infection) and the clinical outcomes were analyzed.

The following laboratory parameters with reference ranges and indices such as Thyroid - Stimulating Hormone (TSH: 0.35–4.94 mIU/L), free Thyroxine (fT4: 11.5 to 22.7 pmol/L), free Triiodothyronine (fT3: 3.5 to 6.5 pmol/L), calcium (Ca: 8.4 to 10.2 mg/dL), aspartate aminotransferase (AST 5-34 u/L), alanine aminotransferase (ALT 0-55 u/L), gamma glutamyltransferase (GGT 12-64 u/L), alkaline phosphatase (ALP 40-150 u/L), total & direct bilirubin (T. Bil: 0.2-1.2 mg/dL, D. Bil: 0-0.5 mg/dL) levels, and complete blood count levels. These data were noted pre and postoperatively.

Informed consent was taken from all the patients before treatment and femoral or subclavian dialysis catheters were placed. Apheresis was performed using a Fresenius Comtec with continuous flow; 1 to 1.5 L of plasma was exchanged in every session. The average blood-flow rate was adjusted at 55-70 mL/min. The replacement fluids were FFP or 5% human albumin

solution in saline. All the patients were monitored during the TPE sessions for possible adverse reactions or changes in hemodynamic stability. The patients serum hormone levels were checked after the procedure and those with acceptable values were proceeded to surgery. But, those with high serum levels underwent subsequent TPE treatment.

TPE's adverse effects were noted. Serum total calcium, free T3, and free T4 levels were noted at 6 hours after TPE sessions. Serum total calcium levels were noted at 24 and 48 hours postoperatively. Patients with hypocalcemia were treated with calcium and vitamin D replacement. In order to detect RLN palsy indirect laryngoscopy was done preoperatively.

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Statistical analyses were performed with Statistical Package for the Social Sciences Software (version 20; SPSS, Inc. Chicago, IL). Non-parametric tests (Wilcoxon and/or Kruskal Wallis tests) were performed for the statistical analysis in group comparisons. All the continuous variables are presented as median.

RESULTS

Our patients were 15 (55.6%) female, 12 (44.4%) male with a mean age of 44 (23-82) years. The most common presenting complaints were weight loss and palpitations. The causes of thyrotoxicosis were: 16 (59.3%) Graves' disease, 7 (25.9%) toxic multinodular goitre (TMG), and 4 (14.8%) amiodarone-induced thyrotoxicosis (AIT) cases. The indications for apheresis were medical treatment failure in 15 (55%) patients (11 Graves' disease, 4 TMNG), anti-thyroid drug adverse effects in 6 (22%) patients (3 TMNG, 3 Graves' disease) and thyroid storm in 6 (22%) patients (4 AIT, 2 Graves' disease). The most common anti-thyroid drug side effects were agranulocytosis and toxic hepatitis. Medical treatment failure was defined as patients who do not enter remission despite adequate time and the dose of anti-thyroid therapy. Thyroid gland was palpable in 11 (40.7%) patients, whereas 5 (18.5%) patients with Graves' disease had ophthalmopathy. The clinical and demographic characteristics of the patients are described in Table 1.

As the TPE solution, FFP was used in 19 patients, while 5% human albumin was used in the remaining 8 patients. The average number of TPE sessions were 3 (2-17). The pre-TPE mean free thyroxine (fT4) level

was 12 (5-46) pmol/L while free tri-iodothyronine (fT3) level was 34 (17-141) pmol/L. The post-TPE fT3 level was 6 (3-10) pmol/L, while the fT4 level was 21 (12-41). There was one case of allergic reaction during the procedure. Total thyroidectomy was performed in all patients. In the postoperative follow-up, there was transient hypocalcemia in 8 (29%) patients, permanent hypocalcemia in 1 (3.7%) patient, and surgical site infection in 1 (3.7%) patient. The pathology revealed papillary thyroid carcinoma in 6 (22%) patients.

DISCUSSION

Endocrine and metabolic emergencies are rare clinical conditions that constitute less than 1% of hospital admissions (13-14). Although rare, thyrotoxicosis and thyroid storm are serious clinical conditions that carry considerable life-threatening morbidity and mortality if left untreated (15). There are 3 possible treatment options for thyrotoxicosis; antithyroid drugs, surgery, and radioactive iodine ablation treatment (1). The choice of treatment is dictated by the etiology of the disease and the condition of the patient. Antithyroid drugs are the first-line treatment for hyperthyroidism. However, side effects such as drug-related hepatotoxicity and agranulocytosis (<1%) or hormone suppression failure

despite drug use may limit the use of these drugs 16. In this study, the two main etiologic indications for TPE were medical treatment failure in 15 (55%) and adverse effects of the antithyroid drugs in 6 (22%) patients.

Thyroidectomy is a definitive and effective treatment option in the management of thyrotoxicosis. In the management of thyrotoxicosis, thyroidectomy is indicated in clinical conditions such as treatment-limiting adverse drug reactions or medical treatment failure, presence of suspicious thyroid nodule or malignant cytology, and iodine-induced thyrotoxicosis. But normal thyroid hormone levels should be attained before surgery because thyrotoxicosis carries an increased risk of morbidity and mortality due to thyroid storm (10,17).

During preoperative management, alternative treatments have become a regular option in cases where conventional treatment methods fail due to treatment-related complications. TPE is one of these alternative treatment options. Since Ashkar *et al.* (6) first demonstrated the use of TPE in thyroid storm treatment in 1970, more case presentations and larger patient series have been published and shared in the literature (3,9-11).

TPE is used in an array of diseases. The basic principle of TPE is the rapid extraction of harmful components from the blood plasma and the simultaneous replacement of plasma proteins with colloid solutions

Table 1. Demographic and clinical characteristics (n: 27)

Variables	Findings
Female (n (%))	15 (55.6)
Age (years) (median)	44 (23-82)
Disease (n (%))	
Graves' disease.	16 (59.3)
Toxic multinodular goiter	7 (25.9)
Amiodarone-induced thyrotoxicosis.	4 (14.8)
Plasmapheresis Indications (n (%))	
Drug ineffectiveness	15 (55.6) (11 GD, 4TMG)
Drug side effect	6 (22) (3 GD, 3 TMG)
Thyroid storm	6 (22) (4 AIT, 2 GD)
Number of plasmapheresis sessions (median)	3 (2-17)
Changes in Thyroid Hormone Concentrations (median)	
Before TPE	
FT3 (pmol/L)	12 (5-46)
FT4 (pmol/L)	34 (17-141)
After TPE	
FT3 (pmol/L)	6 (3-10)
FT4 (pmol/L)	21 (12-41)
Operation (n (%))	27 (100)
Complication (n (%))	
Transient hypocalcemia	8 (29)
Bleeding	1 (3.7)
Wound infection	1 (3.7)
Persistent hypocalcemia	1 (3.7)

GD: Graves' disease, TMG: Toxic multinodular goiter, AIT: Amiodarone-induced thyrotoxicosis, TPE: Therapeutic plasma exchange, FT3: Free triiodothyronine, FT4: Free thyroxine.

like albumin or fresh frozen plasma. The application principle in thyrotoxicosis is the extraction of protein-bound thyroid hormones from the plasma as 99% of thyroid hormones in the circulation are bound to plasma proteins. TPE extracts these hormones from the plasma and replaces the proteins with colloid agents using FFP or 5% human albumin in the process. FFP is cheaper and easier to use but carries higher complications (infections, citrate-related paresthesia, muscle cramps, urticaria, anaphylaxis, etc) risks than 5% human albumin. However, The Japanese Endocrine Society and Thyroid Association recommend the use of fresh frozen plasma because of high levels of thyroid-binding globulin in thyroid crisis 18. In this series, FFP was used in 19 patients, 5 of whom were in thyroid crisis. One of the patients in the FFP group developed an allergic reaction that was successfully managed medically. Moreover, in the postoperative follow-up, there was transient hypocalcemia in 8 (29%) patients, permanent hypocalcemia in 1 (3.7%) patient, and surgical site infection in 1 (3.7%) patient. The surgical site infection was successfully managed with antibiotics while the postoperative haemorrhage case did not require surgical intervention. The rate of surgical complications such as hypocalcemia, haemorrhage, and surgical site infections, was relatively higher in TPE patients compared to our clinical studies of standard patients and other studies in the literature (19). This can be attributed to the effects of the TPE.

TPE not only extracts harmful components but also alters the levels of functional plasma components such as antibodies, catecholamines, cytokines, and other useful proteins. But, it is an effective treatment option because it rapidly lowers the hormone levels in a relatively safe manner. However, the procedure also carries complications such as hypotension, haemolysis, allergic reactions, catheter-related complications, coagulopathy, surgical site infections, hypocalcemia (20), and mortality (0.03-0.05%) in rare cases (21).

TPE removes the hormones together with the binding proteins, but its effects are mostly transient as hormone levels rebound in a matter of days (22-25). Therefore, hormone levels should be monitored daily, and the patients operated when the desired levels are attained. In this study, hormone levels were monitored daily during the TPE, and patients operated on when the desired levels were attained. There is no consensus on the adequate number of TPE sessions or stipulated time to end TPE treatment for thyrotoxicosis. But, the mean TPE sessions range from 1-6 in the literature on the same. In this study, the mean number of sessions was 3 (2-18).

The original reason for TPE in thyrotoxicosis management is thyroid storm. However, in our modern patient management, most patients are diagnosed in time before hormone levels are astronomically high and effectively managed with medical or surgical interventions. Therefore, TPE is preserved for patients who do not either benefit from conventional treatments or those in need of hormonal control to euthyroid levels before the surgery. It is mandatory that euthyroid hormone levels must be attained preoperatively to reduce gland vascularity for well-defined surgical planes and significant reduction of perioperative high mortality rates (up to 30%) associated with thyroid storm (26).

The evidence level of studies on the use of TPE for thyroid storm management is low. The main reason for this is low incidence of thyroid storm coupled with improved diagnostic means that diagnose thyrotoxicosis early for effective treatment.

The American Society for Apheresis (ASFA) guidelines have in 2019 updated the recommendations for the use of TPE in thyroid storm from category III to category II. However, this is not applicable for hyperthyroidism with no accompanying thyroid storm. These guidelines have similarities to the guidelines prepared by The Japan Thyroid Association and Japan Endocrine Society in 2016 (18). The Japanese guidelines recommend the use of TPE in thyroid storm refractory to 24-48 hours of conventional treatment or causing acute liver failure.

Because of the rare use of TPE for treatment of thyrotoxicosis, randomized controlled studies on its efficacy cannot be performed yet. Hence, TPE use for thyrotoxicosis is not in the routine treatment guidelines. A prospective randomized trial should give high evidence level on this topic, and trials with enough patients to provide this level of evidence seem possible in the near future. However, due to the aforementioned limitations and high cost, TPE should be individualized treatment for now.

As per the available literature, this study boasts the second-highest number of patients compared to the other studies on this topic. But, unlike other similar studies, the patients in this study have all subsequently undergone thyroidectomy. The patients who did not receive surgical treatment after the TPE were excluded from the study. Therefore, in this study, TPE was a preoperative step for patients earmarked for thyroidectomy after the medical management has failed. This study, similarly to a study by Simsir *et al.* (3) with a larger cohort of patients, shows that TPE is a safe and effective alternative treatment for thyrotoxic patients.

The majority of published studies with a large cohort of patients on this topic are from hospitals in Turkey (3,9-11). This is largely attributable to the high number of thyrotoxicosis cases in Turkey and the fact that the national insurance covers TPE indication for thyrotoxicosis hence alleviating cost worries.

In conclusion, TPE is an invasive procedure with related morbidities and mortalities and also with efficacy affected by multiple factors. Therefore, it should not be first-line therapy for thyrotoxic patients or thyroid storm. But, it is an effective preoperative bridge where conventional management options are inadequate due to complications or treatment failure. In this study, it has been shown that the preoperative use of TPE in thyrotoxicosis and thyroid storm is safe and effective independent of the etiology. However, in summation, the existing studies indicate that a controlled, randomized, prospective study is needed to attain the level of evidence to recommend the use of TPE for the routine management of thyrotoxic patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

- Cooper, DS. Hyperthyroidism. *Lancet* 2003;362(9382):459–468.
- Fisher, JN. Management of thyrotoxicosis. *South Med J* 2002;95(5):493–505.
- Simsir IY, Ozdemir M, Duman S, Erdogan M, Donmez A, Ozgen AG. Therapeutic plasmapheresis in thyrotoxic patients. *Endocrine* 2018;62:144–148.
- Gündoğdu AS, Kabalak T, Kamel N, Erdoğan G. *Tiroid Hastalıkları. İç hastalıkları*, 1. Ed., MD: Medikal&Nobel Tıp Kitapevi, İstanbul; 2008.
- Schlienger JL, Faradji A, Sapin R, Blickle JF, Chabrier G, Simon C, Imler M. Treatment of severe hyperthyroidism by plasma exchange. Clinical and biological efficacy. 8 cases. *Presse Med* 1985;14(23):1271–1274.
- Ashkar FS, Katims RB, Smoak WM, Gilson AJ. Thyroid storm treatment with blood exchange and plasmapheresis. *JAMA* 1970;214(7):1275–1279.
- De Rosa G, Testa A, Menichella G, Cecchini L, Cavallaro A, Mantovani M, Mango G. Plasmapheresis in the therapy of hyperthyroidism associated with leukopenia. *Haematologica* 1991;76:72–74.
- Braithwaite SS, Brooks MS, Collins S, Bermes EW. Plasmapheresis: an adjunct to medical management of severe hyperthyroidism. *J Clin Apher* 1986;3(2):119–123.
- Ezer A, Caliskan K, Parlakgumus A, Belli S, Kozanoglu I, Yildirim S. Preoperative therapeutic plasma exchange in patients with thyrotoxicosis. *J Clin Apher* 2009;24(3):111–114.
- Keklik M, Kaynar L, Yilmaz M, Sivgin S, Solmaz M, Pala C, Aribas S, Akyol G, Unluhizarci K, Cetin M, Eser B, Unal A. The results of therapeutic plasma exchange in patients with severe hyperthyroidism: a retrospective multicenter study. *Transfus Apher Sci* 2013;48(3):327–330.
- Ozdemir Baser O, Cetin Z, Catak M, Koseoglu D, Berker D. The role of therapeutic plasmapheresis in patients with hyperthyroidism. *Transfus Apher Sci* 2020;102744.
- Agha R, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C, Mathew G, for the STROCSS Group. The STROCSS 2019 Guideline: Strengthening the Reporting of Cohort Studies in Surgery. *International Journal of Surgery* 2019;72:156-165.
- Sarlis NJ and Gourgiotis L. Thyroid emergencies. *Rev Endocr Metab Disord* 2003;4(2):129–136.
- Wartofsky L. Thyrotoxic storm. In: Braverman LE, Utiger RD, editors. *Werner's and Ingbar's the thyroid: a fundamental and clinical text*. Philadelphia, MD: Lippincott Williams & Wilkins; 2000.
- Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, Sarode R, Schwartz J, Weinstein R, Shaz BH. Apheresis applications committee of the American Society for Apheresis. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the apheresis applications committee of the American Society for Apheresis. *J Clin Apher* 2010;25:83–177.
- Cooper DS. Antithyroid drugs. *N Engl J Med* 2005;352:905-917.
- Langley RW, Burch HB. Perioperative management of the thyrotoxic patient. *Endocrinol Metab Clin North Am* 2003;32(2):519-534.
- Satoh T, Isozaki O, Suzuki A, Wakino S, Ibuti T, Tsuboi K, Kanamoto N, Otani H, Furukawa Y, Teramukai S, Akamizuet T. Guidelines for the management of thyroid storm from the Japan Thyroid Association and Japan Endocrine Society. *Endocr J* 2016;2016:EJ16–0336.
- Yabanoglu H. 23 saatlik /Günübirlık Hastanede Kalış Süresi ile Yapılan Tiroidektomi Vakalarımız ve Klinik Sonuçlarımız. *Çukurova Anestezi ve Cerrahi Bilimler Dergisi* 2019;2(2):53-60.
- Yeh JH, Chen WH, Chiu HC. Complications of double-filtration plasmapheresis. *Transfusion* 2004;44:1621-1625.
- Diamond TH, Rajagopal R, Ganda K, Manoharan A, Luk A. Plasmapheresis as a potential treatment option for amiodarone-induced thyrotoxicosis. *Intern Med J* 2004;34(6):369-370.
- Szczepiorkowski ZM, Bandarenko N, Kim HC, Michael L, Linenberger, Marques MB, Sarode R, Schwartz J, Shaz BH, Weinstein R, Wirk A, Winters JL. American Society for Apheresis; Apheresis Applications Committee of the American Society for Apheresis. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the apheresis applications committee of the American Society for Apheresis. *J Clin Apher* 2007;22:106–175.
- Binimelis J, Bassas L, Marruecos L, Domingo ML, Madoz P, Armengol S, Mangués MA, Leiva AD. Massive thyroxine intoxication: evaluation of plasma extraction. *Intensive Care Med* 1987;13:33–38.
- Rajeswaran C, Shelton RJ, Gilbey SG. Management of amiodarone-induced thyrotoxicosis. *Swiss Med Wkly* 2003;133:579–585.
- Aghini-Lombardi F, Mariotti S, Fosella PV, Grasso L, Pinchera A, Braverman LE, Martino E. Treatment of amiodarone iodine-induced thyrotoxicosis with plasmapheresis and methimazole. *J Endocrinol Invest* 1993;16:823–826.
- Mc Gonigle AM, Tobian AAR, Zink JL, King KE. Perfect storm: Therapeutic plasma exchange for a patient with thyroid storm. *J Clin Apher* 2018;33(1):113-116.
- Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, Pham HP, Schneiderman J, Witt V, Wu Y, Zantek ND, Dunbar NM, Schwartz J. Guidelines on the use of therapeutic apheresis in clinical practice evidence based approach from the writing committee of the American Society for Apheresis: the eighth special issue. *J Clin Apher* 2019;34:171–354.