



## Retrospective Evaluation of the Efficiency of Therapeutic Plasmapheresis in Thyrotoxic Patients

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### ABSTRACT

**Background** Therapeutic plasma exchange (TPE) is a treatment method that can be used to provide euthyroidism before permanent treatment in patients with severe thyrotoxicosis, in cases of thyroid storm and in cases where antithyroid drug (ATD) cannot be used due to side effects or ineffectiveness. This study presented our results and experience on TPE in thyrotoxic patients.

**Material and Methods** The data of 10 patients who underwent plasmapheresis for thyrotoxicosis in Bursa Uludag University Faculty of Medicine Endocrinology Clinic were retrospectively analyzed and compared with the literature.

**Results** Ten patients, 6 female and 4 male, were included. The cause of hyperthyroidism was Graves' disease in 8 patients and toxic multinodular goiter (TMNG) in 2 patients. It was observed that the reason for applying plasmapheresis in the patients was primarily due to toxic hepatitis. The mean number of plasmapheresis required to maintain euthyroidism was 4 (1-8). While no difference was found between the thyroid-stimulating hormone (TSH) results before and after TPE, free T4 (fT4) and free T3 (fT3) values were statistically significantly lower after TPE. It was observed that the leukocytes were considerably higher after TPE and the sodium and calcium values were markedly lower after TPE in the patients. After TPE, 7 patients underwent total thyroidectomy, 1 patient received radioactive iodine (RAI) treatment, and 2 were discharged with ATD treatment.

**Conclusions** TPE is an effective and safe treatment option that can be applied in cases where it is necessary to provide rapid euthyroidism before permanent treatments or non-thyroid surgical procedures or to treat life-threatening thyrotoxicosis. It requires experience in application and follow-up and provides rapid euthyroidism when performed in experienced centres.

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## Introduction

Thyrotoxicosis; refers to the state of high thyroid hormone levels in the blood. It is called thyrotoxicosis with hyperthyroidism if it is caused by increased synthesis and secretion of thyroid hormones.<sup>1</sup> The most common causes of thyrotoxicosis with hyperthyroidism are Graves' disease, toxic adenoma, and toxic multinodular goiter (TMNG). The three most commonly used methods of treatment are antithyroid drug (ATD), radioactive iodine (RAI) and surgery. After patients are rendered euthyroid with ATD, permanent treatments such as RAI or surgery can be applied in necessary cases.<sup>2</sup> In patients with severe hyperthyroidism, in cases of thyroid storm and in cases where ATD cannot be used due to side effects or ineffectiveness, plasmapheresis therapy can be used to provide euthyroidism before permanent treatment.<sup>3-8</sup> Therapeutic plasma exchange (TPE) is the process of replacing patient plasma with albumin or fresh frozen plasma (FFP). During this treatment, thyroid hormones, high molecular weight substances, autoantibodies, immune complexes, cytokines, catecholamines and thyroid-binding globulins are also cleared from the patient's blood.<sup>9</sup> Anaphylaxis, hypotension, hypocalcemia, catheter-related complications and coagulation disorders may develop due to plasmapheresis.<sup>10,11</sup> This study aimed to retrospectively evaluate the pre-and post-TPE results of patients who underwent TPE for thyrotoxicosis with hyperthyroidism in our center and the complications that developed during the procedure.

## Material and Methods

Ten patients who underwent TPE treatment for thyrotoxicosis with hyperthyroidism between January 2016 and December 2021 at Bursa Uludag University Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism Diseases were included in the study after the approval of the Ethics Committee. Patients with insufficient follow-up data were excluded from the study. Demographic and clinical characteristics of the patients, thyroid function tests and other biochemical parameters before and after TPE, treatment types after TPE,

and the pathology results of the patients who went to surgery were evaluated retrospectively.

Plasma volume of the patients was calculated according to gender, height, weight and hematocrit information. The blood flow rate was set as 55-70 ml/min. Spectra Optia (Japan) devices were used for apheresis. While predominantly using FFP for apheresis, albumin was performed when there was difficulty in obtaining FFP, or in patients with an allergic reaction after FFP or multiple drug allergies. Vital signs were obtained at the beginning and end of each procedure, and patients were monitored for adverse events during apheresis procedures. Before each plasmapheresis, the procedure risks were explained in detail and then written informed consent was obtained from all patients. Intravenous 10% calcium gluconate was given to all patients to avoid severe hypocalcemia. Each apheresis session lasted 2.5-3 hours. Plasmapheresis was administered daily or every other day until normal thyroid function or clinical improvement was achieved.

### *Statistical Analysis*

For statistical analysis, data were recorded in SPSS 25 (Statistical Package for the Social Sciences) software. Shapiro Wilk test was used for normality tests, and Student T-test was used for parametric tests in group comparisons. Non-parametric tests were analyzed with the Mann Whitney U test, and 2 dependent non-parametric samples were analyzed with the Wilcoxon test. Values with a p-value of <0.05 were considered statistically significant.

## Results

Six of the 10 patients included in the study were female, and 4 were male, and the mean age of the patients was  $44 \pm 17.1$  years. Mean age was found to be  $38.3 \pm 17$  years in women and  $52.5 \pm 15.3$  years in men. The cause of hyperthyroidism was Graves' disease in 8 patients and TMNG in 2 patients. Of the 8 Graves' patients, 5 were women. The median time since diagnosis was 3.5 (0-240) months. While 60% of the patients had weight loss and palpitations as main symptoms, 40% had sweating and tremor. It was observed that the most common reason for patients to undergo plasmapheresis was toxic hepatitis, followed by

agranulocytosis, thyroid storm, unresponsiveness to high-dose antithyroid therapy, and to provide euthyroidism before emergency bypass surgery (one patient). The mean hospital stay of the patients was  $14.3 \pm 5.4$  days, and the mean number of plasmapheresis sessions required to maintain euthyroidism was  $4 \pm 2.35$  (min 1-max 8 sessions). Plasmapheresis sessions were performed with FFP in 7 patients and albumin in 1 patient. Both FFP and albumin were used in 2 patients. Due to the problem experienced in obtaining FFP in 1 patient, albumin was performed once and then FFP was used. In the other patient, first FFP was given

and then continued with albumin after a minor allergic reaction. All patients used methimazole as ATD treatment before hospitalization, except for one unfollowed patient, and methimazole was discontinued in one patient just before hospitalization due to pregnancy. The median dose of methimazole they used was 15 (10-80) mg. The beta-blocker dose used before TPE was  $71.5 \pm 45.34$  mg, and after TPE  $62 \pm 46.61$  mg, no difference was found between the two groups ( $p=0.488$ ). Details of patient characteristics and treatment data are given in Table 1.

**Table 1.** Patient characteristics and treatment data of patients who underwent therapeutic plasmapheresis for thyrotoxicosis with hyperthyroidism.

Variables	Findings
Female gender n (%)	6 (60)
Age (year)	$44 \pm 17.1$
Cause of hyperthyroidism n (%)	
Graves	8 (80)
TMNG	2 (20)
Reason for plasmapheresis n (%)	
Toxic hepatitis	3 (30)
Agranulocytosis	2 (20)
Thyroid storm	2 (20)
Unresponsiveness to ATD	2 (20)
Non-thyroid emergency surgery	1 (10)
Hospitalization duration (day)	$14.3 \pm 5.4$
Number of plasmapheresis sessions (n)	$4 \pm 2.35$
Time since diagnosis (month)	3.5 (0-240)
Additional treatment n (%)	
Lugol	7 (70)
Steroid	4 (40)
Definitive treatment n (%)	
Surgical	7 (70)
RAI	1 (10)
ATD	2 (20)

Data were given as mean  $\pm$  standard deviation, median (minimum:maximum) or frequency. n: number, TMNG: toxic multinodular goiter, ATD: antithyroid drug, RAI: radioactive iodine.

While no difference was found between TSH results before and after TPE ( $p=0.14$ ), fT4 and fT3 values were found to be statistically significantly lower after plasmapheresis ( $p=0.005$ ,  $p=0.005$ , respectively), there was no statistically significant difference between TSH receptor antibody levels (TRAb) before and after TPE in patients with Graves' disease ( $p=0.18$ ). The changes in thyroid hormone levels are shown in Table 2.

Patients had significantly higher leukocytes after TPE ( $p=0.011$ ) and substantially lower sodium and calcium values after TPE ( $p=0.01$ ,  $p=0.04$ , respectively), but they were not below the normal laboratory range and did not have a clinical effect. After TPE, 7 patients underwent total thyroidectomy, 1 patient received RAI treatment, and 2 were discharged with ATD treatment. The pathology of all 7 patients who underwent surgery was benign. Except for minor allergic reactions in 2 patients, no serious complications related to TPE were observed. Tables 3 and 4 show changes in complete blood count and biochemical parameters.

## Discussion

In this study, we presented the data of 10 patients who underwent TPE treatment for thyrotoxicosis with hyperthyroidism. ATD, surgery and RAI constitute the three main treatment strategies used in thyrotoxicosis.<sup>12</sup> In cases of inadequate response to ATD treatment or side effects related to ATD, plasmapheresis can be used to provide euthyroidism before permanent treatment.<sup>13,14</sup>

Statistically, our study found a significant decrease in fT3 and fT4 hormone levels after plasmapheresis, similar to the two studies conducted in our country.<sup>15,16</sup> Another study from our country indicated a decrease in free hormone levels with no significant statistical difference.<sup>17</sup> The mean number of plasmapheresis required to provide euthyroidism in our patients was 4, and it has been found to be similar to the literature.<sup>15,16</sup> Although free thyroid hormone levels could not be brought to the normal laboratory range in three of our patients, the clinical findings of thyrotoxicosis were improved with plasmapheresis in all of our patients.

Hepatotoxicity is a side effect that can be seen due to ATD, and although cholestatic hepatitis is more common due to methimazole, toxic hepatitis can also be seen. A significant decrease in liver enzymes after plasmapheresis was reported in different studies, but this did not make a statistically significant difference.<sup>1,18</sup>

Agranulocytosis is a rare but severe life-threatening side effect that can be seen in 0.2-0.5% of ATD. In the literature, plasmapheresis has been found to be an effective and safe treatment option in cases with thyrotoxicosis who cannot use ATD due to agranulocytosis.<sup>6,7,13,19</sup> In our study, plasmapheresis was performed in two of our patients due to ATD-related agranulocytosis, and a significant decrease in free thyroid hormone levels was achieved. While one of our patients did not need granulocyte colony-stimulating factor (GCSF), the other patient was given GCSF treatment because neutropenic fever was accompanied.

**Table 2.** Data of thyroid function tests in patients who underwent therapeutic plasmapheresis for thyrotoxicosis with hyperthyroidism.

Variable (unit)	Pre-TPE	Post-TPE	Normal range	p value
TSH (mU/L)	0.009 (0.002-0.009)	0.009 (0.002-0.22)	0.35-4.94	0.14
fT4 (ng/dL)	3.04±1.21	1.55 (0.7-3.6)	1.71-3.71	0.005
fT3 (ng/dL)	10.8 (6.4-31)	3.95±1.9	0.7-1.48	0.005

Data were given as mean±standard deviation or median (minimum:maximum).

TSH: thyroid stimulating hormone, fT4: free T4, fT3: free T3, PTE: therapeutic plasma exchange.

**Table 3.** Complete blood count data in patients undergoing therapeutic plasmapheresis for thyrotoxicosis with hyperthyroidism.

Variable (unit)	Pre-TPE	Post-TPE	Normal range	p value
WBC (10 <sup>9</sup> /L)	7.4±3.4	11.2±3.1	1.3-3.8	0.011
Hb (g/dL)	12.2±1.48	12.4±1.3	12.5-16.5	0.65
Htc (%)	36.9 ±4.7	36.6(34.7-46.9)	33-44	0.20
Plt (10 <sup>9</sup> /L)	254±82.5	245±76	145-400	0.63

Data were given as mean±standard deviation or median (minimum:maximum).

WBC: leukocyte, Hb: hemoglobin, Htc: hematocrit, Plt: platelet, PTE: therapeutic plasma exchange.

**Table 4.** Biochemical parameters in patients who underwent therapeutic plasmapheresis for thyrotoxicosis with hyperthyroidism.

Variable (unit)	Pre-TPE	Post-TPE	Normal range	p value
Urea (mg/dL)	29.4 (21-66)	31 (16.4-63)	17.9-54.9	0.81
Creatinine (mg/dL)	0.55 (0.4-1.5)	0.5 (0.51-48)	0.7-1.1	0.59
AST (U/L)	22 (10-72)	25.1 ±12.1	13-30	0.44
ALT (U/L)	29.5 (9-289)	28 (16-104)	9-57	0.85
Total bilirubin (mg/dL)	0.55 ± 0.19	0.52±0.2	0.2-1.2	0.78
Direct bilirubin (mg/dL)	0.2 (0.1-0.4)	0.20±0.07	0-0.5	0.38
Na (mmol/L)	139.3±2	137±1.56	136-145	0.01
K (mmol/L)	4.4 ±0.36	4.2±0.3	3.5-5.1	0.07
Ca (mg/dL)	9.3±0.3	9±0.48	8.8-10	0.04
Albumin (g/L)	38.9±3.2	38.1±4.55	40-50	0.64
INR	1 (0.86-2)	0.95 (0.90-1.14)	0.85-1.15	0.46

Data were given as mean±standard deviation or median (minimum:maximum).

AST: aspartate aminotransferase, ALT: alanine aminotransferase, Na: sodium, K: potassium, Ca: calcium, INR: international normalized ratio, PTE: therapeutic plasma exchange.

Thyroid storm is seen in 0.22% of all thyrotoxicosis cases, and its mortality rate varies between 8-30%.<sup>20</sup> Conventional treatments such as ATD, steroid and potassium iodide are used as first-line treatment, but patients with severe symptoms despite these treatments or for whom these treatments are contraindicated should undergo plasmapheresis.<sup>5,21,22</sup> Two of our patients with a previously known diagnosis of Graves' were taken to plasmapheresis because of thyroid storm. One of our patients was a patient who voluntarily

stopped taking the drug and the follow-up, and the other patient was a patient who presented with vaginal bleeding in the first trimester of pregnancy and had significant thyrotoxicosis findings. Although TRAb levels were also high at the time of admission, invasive molar pregnancy was detected in the patient in the follow-up, and she received surgical and chemotherapy treatments for a molar pregnancy. It was thought that molar pregnancy together with Graves' activation might affect developing thyrotoxicosis in this patient.

There are cases in the literature who underwent plasmapheresis due to molar pregnancy.<sup>23,24</sup> One of our patients had plasmapheresis to provide rapid euthyroidism before coronary bypass surgery. There are cases in the literature who underwent plasmapheresis before non-thyroid surgery, as in our case.<sup>17,25</sup>

Histopathologically, no malignancy was detected in any of our patients who underwent thyroidectomy. In the literature, there are also cases with malignancy in Graves' patients who underwent thyroidectomy after plasmapheresis (17.5%), and the majority of them were reported as thyroid papillary carcinoma.<sup>16,26</sup>

In our study, no significant decrease was found in hemoglobin and hematocrit levels after plasmapheresis. There is a study in the literature that supports our study.<sup>15</sup> On the contrary, there is a study that found a statistically significant decrease, but in this study, a reduction was not found to create a need for replacement in patients.<sup>16</sup> In addition, leukocyte level was found to be statistically significantly higher after plasmapheresis in our study. Similar to our research, there is a study in the literature with leukocyte elevation after plasmapheresis. It was thought to be due to a partial decrease in the metabolism of neutrophils in the foreground.<sup>27</sup> In another study in which plasmapheresis was performed due to the side effect of toxic hepatitis, leukocyte elevation was observed after plasmapheresis, as in our research. Still, no statistically significant difference was found.<sup>14</sup> In our study, sodium and calcium values after plasmapheresis were significantly lower after plasmapheresis, and this situation was not at a level that would create a clinical effect or require replacement. It is thought that this change in calcium and sodium levels may be related to citrate in patients given FFP and may be dilutional due to the water-retaining effect of albumin in patients using albumin.<sup>28,29</sup>

While serious side effects such as anaphylaxis, catheter infection, and coagulopathy may be seen due to plasmapheresis, no complications were observed in our study except for simple urticarial rash in one patient and itching in one patient.<sup>30</sup>

## Conclusions

TPE is an effective and safe treatment option that can be applied in cases where it is necessary to provide rapid euthyroidism before permanent treatments or non-thyroid surgical procedures or to treat life-threatening thyrotoxicosis. It requires experience in application and follow-up and provides rapid euthyroidism when performed in experienced centres.

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## Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Authors' Contribution

Study Conception: FMS, CE; Study Design: CA, EE; Supervision: CE; Data Collection and/or Processing: OOG, EH; Statistical Analysis and/or Data Interpretation: EA, SC; Literature Review: FMS; Manuscript Preparation: FMS; and Critical Review: CE.

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