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RESEARCH

Effectiveness and safety of therapeutic plasma exchange as a bridging therapy before surgery in patients with medically refractory hyperthyroidism

Medikal tedaviye dirençli hipertiroidi olgularında cerrahi öncesi köprü tedavisi olarak terapötik plazma değişiminin etkinliği ve güvenliği

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Abstract

Purpose: The aim of this study is to evaluate the cost and effectiveness of therapeutic plasma exchange (TPE) treatment applied in patients with hyperthyroidism in whom clinical and biochemical control cannot be achieved with antithyroid drug therapy or who cannot tolerate medical treatment due to severe drug-related adverse effects.

Materials and Methods: This single-center retrospective cohort study included hyperthyroidism patients who underwent TPE to achieve preoperative euthyroidism due to resistance to antithyroid drug therapy or severe adverse drug reactions were evaluated. Thyroid function tests and autoantibody levels were compared before and after plasmapheresis.

Results: The mean age of the 22 patients included in the study was 38.6 ± 15.3. Graves' disease was detected in 72% of the patients, and toxic multinodular goiter in 28%. The indications for plasmapheresis were drug resistance (90.9%), elevated AST–ALT levels (4.5%), and neutropenia (4.5%). A comparison of the biochemical parameters before and after plasmapheresis demonstrated a significant reduction in sT3 and sT4 levels. In contrast, a significant increase in TSH levels was observed after the procedure. Evaluation of autoimmune markers revealed significant decreases in anti-TG, thyroglobulin, and anti-TPO levels.

Conclusion: TPE provides rapid clearance of circulating free thyroid hormones in patients with pharmacotherapy-resistant thyrotoxicosis and represents an effective and safe metabolic stabilization strategy that facilitates safe progression to curative surgery.

Keywords:. Hyperthyroidism, therapeutic plasma exchange, plasmapheresis, thyroidectomy

Öz

Amaç: Bu çalışmanın amacı antitiroid ilaç tedavisi ile klinik ve biyokimyasal kontrol sağlanamayan ya da ciddi ilaç yan etkileri nedeniyle medikal tedaviyi tolere edemeyen hipertiroidi olgularında terapötik plazma değişimi (TPE) tedavisinin etkinliğini ve güvenilirliğini değerlendirmektir.

Gereç ve Yöntem: Bu tek merkezli retrospektif kohort çalışması antitiroid ilaç tedavisine direnç gelişmesi veya ciddi advers etkiler nedeniyle cerrahi öncesi ötiroidi sağlamak amacıyla terapötik plazma değişimi uygulanan hastalar değerlendirilmiştir. Plazmaferez öncesi ve sonrası tiroid fonksiyon testleri ile otoantikor düzeyleri karşılaştırılmıştır.

Bulgular: Çalışmaya dahil edilen 22 hastanın yaş ortalaması 38,6 ± 15,3'tür. Hastaların %72'sinde Graves hastalığı %28'inde toksik multinodüler guatr saptanmıştır. Plazmaferez uygulama nedenleri ilaç direnci (%90,9), AST–ALT yüksekliği (%4,5) ve nötropenidir (%4,5). Plazmaferez öncesi ve sonrası biyokimyasal parametreler karşılaştırıldığında sT3 ve sT4 düzeylerinde anlamlı azalma saptanmıştır. TSH düzeyinde ise işlem sonrası anlamlı bir artış gözlenmiştir. Otoimmünite belirteçleri incelendiğinde anti-TG, tiroglobulin ve anti-TPO düzeylerinde anlamlı azalma görülmüştür.

Sonuç: Terapötik plazma değişiminin farmakoterapiye dirençli tirotoksikoz olgularında akut serbest hormon klerensi sağlayarak hastaların küratif cerrahiye güvenle ulaştırılmasında etkili ve güvenilir bir metabolik stabilizasyon yaklaşımıdır.

Anahtar kelimeler: Hipertiroidi, terapötik plazma değişimi, plazmaferez, tiroidektomi

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INTRODUCTION

Hyperthyroidism is one of the most prevalent endocrine disorders worldwide, with a reported population frequency between 0.8% and 1.4% in iodine-sufficient regions[1,2]. The condition occurs considerably more often in women, and its incidence rises progressively with advancing age[2]. Graves' disease accounts for the majority of cases, followed in decreasing frequency by toxic multinodular goiter and toxic adenoma.[1] The clinical consequences of uncontrolled hyperthyroidism are wide-ranging, but the cardiovascular system bears a particularly heavy burden. Sinus tachycardia is nearly universal in overt disease, and atrial fibrillation occurs in 5% to 15% of patients, with the potential to progress to congestive heart failure, hemodynamic instability, and life-threatening cardiovascular collapse[3,4,5].

Current guidelines recommend three first-line therapeutic strategies: antithyroid drug (ATD) therapy, radioactive iodine (RAI) ablation, and surgical thyroidectomy[6]. In everyday clinical practice, ATD therapy is most commonly chosen as the initial approach, particularly in patients presenting with moderate-to-severe thyrotoxicosis, large goiters, or active thyroid eye disease. Among available agents, methimazole is generally preferred over propylthiouracil because of its more favorable pharmacokinetic profile and once-daily dosing schedule. Propylthiouracil retains clinical relevance in pregnancy and in the acute management of thyroid storm[7].

Despite being the first choice in most clinical settings, ATD therapy carries a meaningful rate of treatment failure and serious adverse events. Drug resistance tends to emerge in patients with markedly elevated initial thyroid hormone concentrations, significantly enlarged glands, nodular thyroid architecture, or a history of non-adherence to prescribed regimens[8]. Serious adverse reactions, including agranulocytosis, hepatotoxicity, and vasculitis, occur in a smaller but clinically important subset of patients and necessitate immediate and permanent discontinuation of the offending agent[9]. When adequate biochemical control cannot be achieved, or when continued medical therapy is no longer safe, definitive treatment with RAI or thyroidectomy becomes necessary[7].

Proceeding to thyroid surgery in the setting of active thyrotoxicosis carries substantial perioperative risk. Surgical stress, anesthetic induction, and intraoperative manipulation of the thyroid gland can precipitate thyroid storm, an acute and potentially fatal decompensation characterized by severe tachycardia, hyperpyrexia, sympathetic hyperactivity, and multiorgan failure. Reported in-hospital mortality rates for thyroid storm range from 8% to 25%, even under intensive supportive care[10]. A systematic review by de Mul et al. confirmed that uncontrolled thyrotoxicosis at the time of surgery is an independent risk factor for perioperative thyroid storm, reinforcing the critical importance of achieving a stable euthyroid state before any elective thyroid procedure[11]. Standard preoperative preparation with ATDs, beta-blockers, and potassium iodide is effective in most patients but fails in those with drug resistance or intolerance, who then require alternative stabilization strategies[12,13].

TPE emerged as a bridging option for patients in whom conventional pharmacological preparation is insufficient or contraindicated[14]. According to evidence-based guidelines published by the American Society for Apheresis (ASFA), TPE is classified as a Category II indication for thyroid storm and refractory hyperthyroidism, with sessions recommended at daily or three-day intervals depending on clinical response[15]. The mechanism of action in this setting is grounded in the physiology of thyroid hormone transport: approximately 99% of circulating thyroid hormones travel bound to carrier proteins, principally thyroxine-binding globulin, transthyretin, and albumin, through non-covalent interactions. During apheresis, the patient's plasma along with these protein-bound hormones is removed and replaced with fresh frozen plasma (FFP), which supplies a new pool of unoccupied binding sites and thereby reduces the concentration of biologically active free hormones (fT3 and fT4)[16]. Beyond direct hormonal clearance, TPE also removes thyroid-stimulating hormone receptor antibodies (TRAb) and proinflammatory cytokines that sustain the autoimmune process in Graves' disease[17,18], and offers a particular advantage in amiodarone-induced thyrotoxicosis by accelerating the elimination of the culprit drug, whose prolonged half-life otherwise makes biochemical control exceptionally difficult[19].

The present study evaluates the role of TPE, which represents a life-saving therapeutic approach that can reduce surgical morbidity, be safely implemented even in the presence of antithyroid drug toxicity, and plays an important role in multidisciplinary

endocrinological management. In patients with thyrotoxicosis who were followed in our clinic, we specifically investigated the effectiveness of preoperative TPE as a bridging therapy prior to thyroidectomy in cases who developed resistance to ATD therapy or were unable to continue medical treatment due to drug-related adverse effects. Despite the established use of TPE in severe thyrotoxicosis, important gaps remain regarding its broader immunomodulatory and anti-inflammatory effects. To address these limitations, we not only assessed changes in thyroid hormone levels but also systematically evaluated autoimmune markers and systemic inflammatory parameters. We hypothesized that TPE would result in a statistically significant reduction in circulating thyroid hormone levels sufficient to allow safe progression to thyroidectomy, with additional beneficial effects on autoantibody levels and inflammatory markers.

MATERIALS AND METHODS

Study design

This retrospective cohort study evaluated patients with pharmacotherapy-resistant or medically intolerant thyrotoxicosis who were assessed and treated at Malatya Training and Research Hospital between 2024 and 2025. Ethical approval was obtained from the İnönü University Clinical Research Ethics Committee (Protocol No: 2024/166; Decision Date: 25 December 2024; Ethics Committee Code: 2024-KAEK-08).

Demographic data, including age and sex, as well as clinical variables such as comorbid chronic diseases, indication for plasmapheresis, and number of treatment sessions, were obtained from the hospital's electronic medical record system.

Sample

Sample size was calculated assuming 80% statistical power, an effect size of 0.5, and a type I error rate of 0.05 for two-sided hypothesis testing. Based on these parameters, the minimum required sample size was estimated to be 23 patients. A total of 22 patients who met the eligibility criteria were ultimately enrolled.

A total of 28 patients with hyperthyroidism who were evaluated for therapeutic plasma exchange (TPE) between [study period] were screened for eligibility. Of these, 6 patients were excluded for the following reasons: active infection (n=4) and thyroid hormone levels outside the predefined indications for TPE (n=2). Consequently, 22 patients were included in the final analysis.

Patients were included if they had hyperthyroidism in whom adequate biochemical control could not be achieved with antithyroid drug therapy or in whom continued medical treatment was not possible due to severe drug-related adverse events.Patients were excluded if they had contraindications to therapeutic plasma exchange, including hemodynamic instability, active sepsis, or significant coagulation disorders.

Therapeutic plasma exchange procedure

All procedures were performed using a continuous-flow cell separator (COM.TEC, Fresenius Kabi AG, Bad Homburg, Germany) operating at a maximum centrifuge speed of 2200 rpm and a maximum load capacity of 3.0 kg. In accordance with standard therapeutic apheresis protocols, a target plasma exchange volume of 1.0–1.5 plasma volumes per session was achieved. FFP was used as the sole replacement fluid in all procedures.

The indication for TPE was determined based on the planned number of sessions, the patient's clinical condition, and the adequacy of peripheral venous access in the upper extremities. For central venous access, a dialysis catheter was placed in the internal jugular or subclavian vein under ultrasound guidance. Correct catheter placement and the absence of procedure-related complications, including pneumothorax, were systematically confirmed by post-procedure chest X-ray.

Anticoagulation of the extracorporeal circuit was achieved using acid citrate dextrose solution A (ACD-A). The total volume of ACD-A administered and the volume of ACD-A returned were automatically calculated by the device's integrated system. To prevent hypocalcemia, continuous calcium supplementation was administered throughout the procedure. The calcium dose was adjusted according to pre-procedure serum calcium levels and the type of replacement fluid used. In general, calcium chloride infusion was performed at a rate of approximately 2 g per hour during sessions involving FFP replacement.

All TPE procedures were performed by an experienced apheresis team (endocrinology specialist, internal medicine resident, nurse, and apheresis technical staff) in accordance with the institution's standard clinical protocols. Each session lasted

approximately 2.5–3 hours. Vital signs were recorded before and after each procedure, and patients were closely monitored for potential side effects throughout the sessions. Prior to the procedure, all patients were given detailed information about the potential risks, and written informed consent was obtained. Following biochemical stabilization, patients were referred for definitive treatment with thyroidectomy.

Outcome measures

The primary biochemical outcome measures of the study were changes in free triiodothyronine (fT3) and free thyroxine (fT4) levels measured before and after TPE. To evaluate treatment response, both absolute and percentage changes in these parameters were calculated.

Secondary outcome measures included changes in biochemical parameters related to thyroid function and autoimmunity. Therefore, levels of thyroid-stimulating hormone (TSH), anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-TG), thyroglobulin, and C-reactive protein (CRP) were analyzed. After biochemical stabilization was achieved through TPE, the patients were referred for thyroidectomy as definitive treatment.

Statistical analysis

Statistical analyses were performed using Jamovi statistical software (version 2.6.44). The normality of continuous variables was assessed using the Shapiro-Wilk test. For variables that did not meet the normality assumption ($p < 0.05$), descriptive statistics were presented as median and interquartile range (IQR). All biochemical parameters measured before and after plasmapheresis (TSH, fT3, fT4, anti-TG, thyroglobulin, anti-TPO, CRP) constituted paired measurements obtained from the same individuals. Since the distributions of the differences between these pre- and post-procedure measurements did not follow a normal distribution, a non-parametric method, the Wilcoxon signed-rank test, was preferred for pre-post comparisons.

The rationale for selecting the Wilcoxon test is threefold: (i) it does not require the normality assumption for the differences between two dependent measurements obtained from the same individuals, (ii) it is robust against outliers, and (iii) it provides reliable results in small-to-moderate sample sizes, which is particularly relevant given the invasive nature of the procedure and its restricted clinical indications. To assess the magnitude of the intervention effect beyond statistical significance, effect sizes were calculated using the rank-biserial correlation coefficient, which is appropriate for the Wilcoxon test. Effect sizes were interpreted as follows: 0.10–0.30 indicated a small effect, 0.30–0.50 a moderate effect, and ≥0.50 a large effect. This approach allowed for the evaluation of both statistical significance and clinical importance of the findings. A two-sided hypothesis testing framework was employed for all analyses, and a p-value of <0.05 was considered statistically significant

RESULTS

A total of 22 patients were included in the study. The mean age of the cohort was 38.6 ± 15.3 years, and the majority of participants were female (72.7%), with men accounting for the remaining 27.3%. Graves' disease was the underlying diagnosis in 72% of patients, while toxic multinodular goiter was identified in the remaining 28%.

With respect to antithyroid treatment at the time of referral, 90.9% of patients were receiving methimazole and 9.1% were receiving propylthiouracil. Drug resistance was the primary indication for plasmapheresis in 90.9% of cases. Elevated transaminase levels (elevated AST and ALT) were the indication in one patient (4.5%), and neutropenia in another (4.5%).

The majority of patients (77.3%) had no comorbid chronic diseases. Among those with additional diagnoses, hypertension was present in 9.1%, chronic obstructive pulmonary disease (COPD) in 4.5%, migraine in 4.5%, and type 1 diabetes mellitus in 4.5%.

Plasmapheresis was performed in one session in 31.8% of patients, two sessions in 59.1%, and three sessions in 9.1%. The overall mean volume of FFP used across all procedures was 24.5 ± 8.72 units. When stratified by session count, the mean FFP volume per procedure was 13.6 ± 1.13 units for single-session patients, 27.8 ± 2.76 units for two-session patients, and 40.5 ± 2.12 units for three-session patients. No procedure-related complications were observed in any patient (Table 1).

Table 1. Sociodemographic and clinical characteristics of the patients

Variables	**Mean±S.D.**	
Age (years)	38.6±15.3	
FFP volume used (total)	24.5±8.72	
Sex	n	%
Male	6	27.3
Female	16	72.7
Antithyroid drug		
Methimazole	20	90.9
Propylthiouracil	2	9.1
Thyroid disease		
Graves' disease	16	72
Toxic multinodular goiter	6	28
Chronic disease		
Hypertension	2	9.1
Chronic obstructive pulmonary disease (COPD)	1	4.5
Migraine	1	4.5
Type 1 diabetes mellitus	1	4.5
None	17	77.3
Indication for plasmapheresis		
Elevated AST–ALT levels	1	4.5
Neutropenia	1	4.5
Drug resistance	20	90.9
Number of plasmapheresis sessions		
1	7	31.8
2	13	59.1
3	2	9.1
Post-plasmapheresis complications		
Hypocalcemia	0	0
Bleeding	0	0
Catheter-related infection	0	0
Total	22	100.0

FFP: Fresh Frozen Plasma, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase

Table 2. Changes in thyroid function tests and autoantibody levels pre- and post-plasmapheresis

	Therapeutic plasmapheresis				
Variable	**Pre-Plasmapheresis Median (IQR)**	**Post-Plasmapheresis Median (IQR)**	**Mean Difference**	**Effect Size***	**p-value**
TSH (mU/L)	0.0050 (0.0000)	0.0052 (0.0107)	-0.0116	-1.000	0.004
fT3 (pg/mL)	21.25 (8.10)	3.02 (1.33)	17.6400	1.000	<0.001
fT4 (ng/mL)	5.62 (2.40)	1.76 (0.60)	3.8450	1.000	<0.001
ANTİ TG (IU/mL)	51.25 (244.82)	43.05 (106.60)	65.1499	0.704	0.004
Tiroglobulin (ng/mL)	19.50 (433.42)	13.85 (113.87)	80.5000	0.889	<0.001
Anti-TPO (IU/mL)	132.00 (139.85)	65.05 (98.77)	62.2000	0.922	<0.001
CRP (mg/L)	0.50 (2.17)	0.20 (0.00)	2.2001	0.912	0.004

TSH: Thyroid Stimulating Hormone, fT3: Free tri-iodothyronine , fT4: Free Tetra-iodothyronine, Anti TG: Anti-Tyroglobulin Antibody, AntiTPO: Anti-thyroid peroxidase, CRP: C-reactive protein

Comparison of biochemical parameters before and after plasmapheresis revealed marked reductions in circulating thyroid hormone levels. Median fT3 decreased from 21.25 to 3.02 ($p < 0.001$), and median fT4 fell from 5.62 to 1.76 ($p < 0.001$). A modest but statistically significant increase in TSH levels was also observed following the procedure ($p = 0.004$). Assessment of autoimmune markers showed that anti-TG, thyroglobulin, and anti-TPO levels all decreased significantly following plasmapheresis ($p = 0.004$, $p < 0.001$, and $p < 0.001$, respectively). CRP, as a marker of systemic inflammation, likewise decreased significantly after TPE ($p = 0.004$). Effect size analysis confirmed a very strong treatment effect for fT3 and fT4, with moderate-to-high effect sizes observed for the autoantibody and inflammatory markers (Table 2, Figure 1).

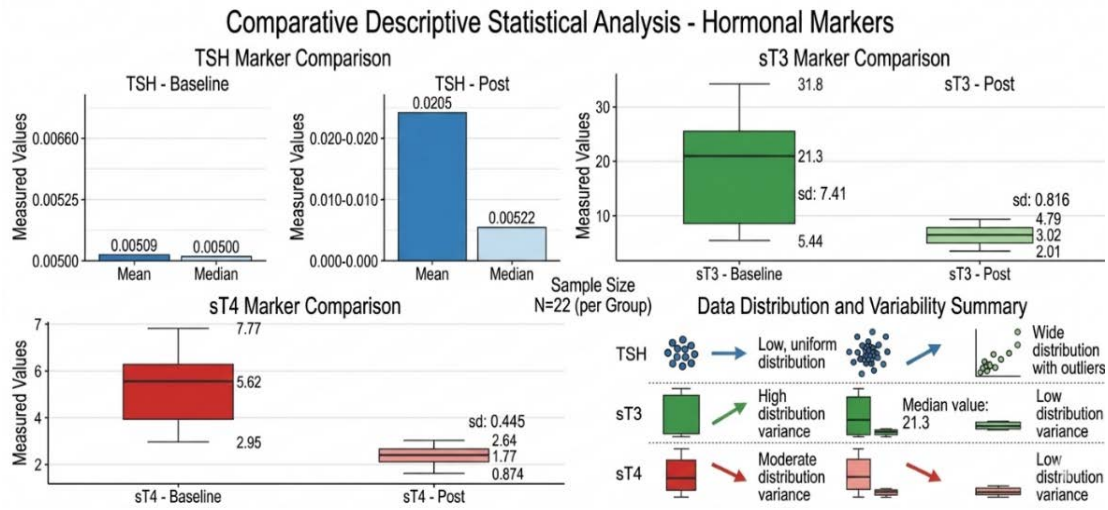


Figure 1. Changes in thyroid function tests pre- and post-plasmapheresis.

DISCUSSION

Hyperthyroidism is characterized by the excessive production and secretion of thyroid hormones. The most common underlying cause is Graves' disease, followed by toxic multinodular goiter and toxic adenoma in decreasing order of frequency[1]. Population-level prevalence estimates range between 0.8% and 1.4%, with higher rates in women and in older age groups[1,2]. The cardiovascular manifestations of hyperthyroidism are particularly prominent, with sinus tachycardia occurring in nearly all patients with overt disease and atrial fibrillation developing in approximately 5% to 15% of cases. If left inadequately treated, these complications may progress to congestive heart failure and significant hemodynamic compromise[3,4].

First-line treatment for hyperthyroidism is based on thionamide agents such as methimazole and propylthiouracil. Methimazole is generally favored because of its superior efficacy, tolerability, and once-daily dosing schedule arising from its longer duration of action. Serious adverse reactions, including agranulocytosis, hepatotoxicity, and vasculitis, may necessitate immediate drug discontinuation. Resistance to antithyroid therapy tends to be associated with markedly elevated initial thyroid hormone concentrations, enlarged or nodular glands, and poor medication adherence[8]. In such cases, definitive treatment with thyroidectomy or RAI becomes necessary[7]. Achieving metabolic optimization during the preoperative period is critical to minimizing the risk of thyroid storm, which can be precipitated by the physiological stress of surgery and anesthetic induction[13].

TPE is widely regarded as a strategic bridging modality in situations where conventional treatment is insufficient or contraindicated[20]. It rapidly reduces circulating thyroid hormone levels and, particularly in Graves' disease, also removes autoantibodies, binding proteins, cytokines, and catecholamines from the circulation[18]. Regarding replacement fluid selection, FFP carries a risk of allergic reactions, while albumin solution has been associated with perioperative

bleeding complications. Given that all patients in this cohort were being prepared for thyroidectomy, FFP was chosen as the preferred replacement fluid for all plasmapheresis procedures[20].

The main findings of our study indicate that TPE demonstrates high biochemical efficacy in terms of both hormonal clearance and autoimmune-inflammatory stabilization. Among the 22 patients who underwent TPE, the indications were resistance to conventional ATD therapy in 20 patients (90.9%), hepatotoxicity in one (4.5%), and agranulocytosis in one (4.5%). A significant reduction in thyroid hormone levels was observed after plasmapheresis (fT3 and fT4, both $p < 0.001$), along with a statistically significant increase in TSH levels ($p = 0.004$). The extremely high effect sizes observed for fT3 and fT4 ($r = 1.000$) can be partly attributed to the limited sample size and to the uniformly directional reduction in hormone levels across all patients. Statistically significant reductions were also detected in anti-TG antibodies ($p = 0.004$, $r = 0.704$), anti-TPO antibodies ($p < 0.001$, $r = 0.922$), thyroglobulin ($p < 0.001$, $r = 0.889$), and CRP ($p = 0.004$, $r = 0.912$). Similarly, Koziak et al.[20] reported reductions of 51.9% in fT4 and 66.6% in fT3 in their scoping review of 42 studies and 234 patients. The reductions observed in our study were somewhat higher, reaching 68.59% for fT4 and 85.76% for fT3, which supports the biochemical effectiveness of TPE in reducing the risk of thyroid storm and is consistent with the range of outcomes reported in the broader literature.

Another study by Saie et al.[17] reported reductions of 48% in free T4 ($p = 0.001$) and 52% in free T3 ($p = 0.0001$) in 22 patients with refractory hyperthyroidism who underwent TPE. Although the fT3 reduction in our study was greater, a significant decrease in fT4 was similarly confirmed. Both studies support the role of TPE in rapidly reducing the intravascular hormone burden, particularly when ATDs are contraindicated or ineffective. The underlying mechanism involves the removal of hormone-bound carrier proteins from the circulation and their replacement with FFP, which provides additional unoccupied thyroxine-binding globulin and thereby increases the binding capacity for free thyroid hormones.[15]

In a study from Turkey, Simsir et al.[21] reported that median fT3 levels decreased from 9.9 pg/mL to 4.0 pg/mL and median fT4 levels fell from 2.9 ng/dL to 1.6 ng/dL following TPE in 46 patients with thyrotoxicosis, with both reductions statistically significant ($p < 0.0001$). Our findings are consistent with these results. In our cohort, mean fT3 decreased by 17.64 units and mean fT4 by 3.845 units (both $p < 0.001$). Regarding underlying diagnosis, Graves' disease accounted for 87% of cases in the study by Simsir et al., compared with 72% in ours, with the remaining six patients diagnosed with toxic multinodular goiter.

One of the notable aspects of our study is its systematic evaluation of the autoimmune marker response following TPE, an area that remains undercharacterized in the literature. While case reports documenting antibody reductions after TPE are available, cohort-level analyses of this scale are rare. The observed reductions in anti-TPO (mean decrease of 62.20 IU/mL) and anti-TG (mean decrease of 65.15 IU/mL) suggest that TPE may modulate the autoimmune component of the disease beyond its immediate hormonal effects. The 2.20 mg/L decrease in CRP ($p = 0.004$) further indicates that TPE may contribute to attenuating the systemic inflammatory response associated with active thyrotoxicosis, which may in turn improve the safety profile of subsequent surgery.

According to ASFA guidelines, TPE is classified as a Category II indication for thyroid storm and refractory hyperthyroidism, with treatment sessions recommended daily or every three days depending on clinical response[15]. The protocol applied in our study, involving the exchange of approximately 1.0 to 1.5 plasma volumes with FFP replacement, was fully consistent with the 2023 ASFA recommendations. In our clinic, sessions were administered at three-day intervals, and no significant correlation was found between the number of sessions (one to three) and the degree of hormonal reduction. This observation suggests that the therapeutic response to TPE may not be strictly dose-dependent, and that maximal hormonal reduction may occur predominantly during the initial sessions, likely reflecting near-complete saturation of the newly supplied binding protein pool. This carries a practical implication: clinical stabilization sufficient for safe surgery may be achievable with a limited number of sessions in patients requiring urgent thyroidectomy.

From a safety standpoint, citrate-induced hypocalcemia is among the most frequently reported complications of TPE. Koziak et al.[20] reported transient hypocalcemia in 13 patients (5.6%) and permanent hypocalcemia in one patient (0.4%). In

contrast, no patient in our cohort developed symptomatic hypocalcemia, which likely reflects the routine prophylactic administration of calcium supplementation during all procedures. Koziak et al.[20] also reported perioperative bleeding in eight patients (3.4%), of whom three required transfusion, and catheter-related infection in three (1.3%). Neither of these complications was observed in our series, supporting the conclusion that TPE performed in experienced apheresis units with standardized protocols carries a favorable safety profile as a preoperative bridging strategy.

The primary limitations of this study are its single-center retrospective design and relatively small sample size, which are partly inherent to the invasive nature of the procedure and its restricted clinical indication. These features limit the generalizability of the findings to other institutional settings. Nevertheless, all patients in the cohort were discharged without complications in the short-term postoperative period following successful surgical stabilization, which supports the clinical effectiveness of the intervention.

In conclusion, TPE is an effective and safe preoperative bridging strategy in high-risk patients with hyperthyroidism who have failed or cannot tolerate antithyroid drug therapy. By facilitating both hormonal clearance and reduction of the autoimmune-inflammatory burden, it can play a central role in achieving the metabolic stability necessary for safe thyroidectomy. The large effect sizes observed in this study and the absence of perioperative complications further support its value as a targeted therapeutic option in carefully selected patients. Nevertheless, standardizing the optimal number of TPE sessions and the most appropriate replacement fluid for patients scheduled for thyroidectomy remains an unresolved question, particularly considering the balance between FFP and albumin in terms of perioperative bleeding risk. The long-term impact of TPE on autoimmune markers, especially whether the reduction in anti-TPO and anti-TG antibodies persists into the perioperative period and is associated with clinical remission, requires further follow-up over the longer term. Cost-effectiveness analyses comparing TPE with pharmacological alternatives would be valuable in guiding resource allocation, especially in centers lacking competent personnel and specialized apheresis infrastructure. In light of all this information, prospective multicenter studies with larger and more diverse cohorts are needed to generate reliable efficacy estimates across different hyperthyroid etiologies and patient profiles.

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