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# Therapeutic Plasmapheresis in Preparation of Toxic Multinodular Goiter for Surgery

## Toksik Multinodular Guatrlı Hastanın Cerrahi Hazırlığında Terapötik Plazmaferez

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**Abstract**

Plasmapheresis is an alternative way of removing excess thyroid hormones from circulation to control the signs and symptoms of hyperthyroidism. The purpose of this report was to determine the effectiveness of plasmapheresis in rapid preparation of toxic multinodular goiter for thyroid surgery. The indications for plasmapheresis were propylthiouracil related ANCA(+) panniculitis and ineffective control of hyperthyroidism with methimazole. Thyroid hormone levels only moderately decreased after 7 sessions of plasmapheresis. She underwent surgery with β-blocker and dexamethasone treatment to avoid thyroid storm in the perioperative period. Surgery was performed uneventfully. Plasmapheresis can be considered a safe and effective method to prepare patients with thyrotoxicosis for surgery when treatment is contraindicated or failed. *Turk Jem 2014; 1: 23-25*
**Key words:** Hyperthyroidism, plasmapheresis, multinodular goiter, thyroid surgery

**Özet**

Hipertiroidinin klinik ve biyokimyasal kontrolünde, dolaşımdaki artmış tiroid hormonlarının temizlenmesi için plazmaferez alternatif bir yol olarak görülmektedir. Amacımız, toksik multinodular guatr saptanan olgumuzda hızlı cerrahi hazırlıkta plazmaferezin etkinliğinin gösterilmesidir. Bu olguda propiltiourasile bağlı ANCA(+) panikülit ve metimazol ile yeterli biyokimyasal kontrolün sağlanamamış olması plazmaferez endikasyonlarını oluşturmaktadır. Olgumuzda 7 seans yapılan plazmaferez sonrası tiroid hormon düzeylerinde orta düzeyli bir düşüş sağlanmıştır. Tiroid krizi gelişiminin önlenmesi için olgu β-bloker ve deksametazon tedavisi altında total tiroidektomiye verilmiştir. Olgunun operasyon sürecinde herhangi bir komplikasyon yaşanmamıştır. Plazmaferez, medikal tedavilerin kontrendike olduğu ya da başarısız kaldığı tirotoksikozlu olgularda, cerrahi hazırlık için kullanılabilecek güvenilir ve etkin bir yöntemdir. *Turk Jem 2014; 1: 23-25*
**Anahtar kelimeler:** Hipertiroidi, plazmaferez, multinodüler guatr, tiroid cerrahisi

## Introduction

Thyrotoxicosis is a condition characterized by excessive amounts of thyroid hormones in bloodstream leading to multisystem involvement with a high mortality rate (1,2). Antithyroid drugs, radioactive iodine and thyroidectomy are three conventional forms of treatment selected according to the specific cause of hyperthyroidism. Thyroidectomy is the definitive treatment especially in patients resistant to other treatment options. Surgical intervention should be performed when the patient is euthyroid to decrease perioperative cardiac risks (3).

Plasmapheresis is a medical procedure that removes the thyroid hormones and antibodies from the bloodstream of patients who are in need of urgent surgical intervention. It has been utilized for the treatment of several immunologic and nonimmunologic disorders such as Graves' disease, intoxication of levothyroxin and amiodarone (4,5).

Here, we report the case of a patient with toxic multinodular goiter (TMNG) who was prepared for surgery by plasmapheresis due to the side effects of antithyroid drugs. In the literature, there are many cases of hyperthyroidism diagnosed as Graves' disease treated with plasmapheresis for the removal of circulating thyroid hormones. However, the role of plasmapheresis in the treatment of TMNG is not fully determined.

## Case Report

A 54-year-old female diagnosed with TMNG was admitted to Sisli Etfal Training and Research Hospital, Endocrinology Clinics because of complicated hyperthyroidism. The patient had been diagnosed with hyperthyroidism seven years ago. She had used different doses of propylthiouracil (PTU) previously for various treatment courses. But no other diagnostic research had been done for the differential diagnosis. She sought further follow-up at another hospital for the diagnostic work-up while on PTU treatment. One week after her thyroid scintigraphy with 99m Technetium, she exhibited dermal lesions on bilateral lower extremities. These were erythematous, tender nodules and plaques healing with postinflammatory hyperpigmentation. She was hospitalized and PTU was stopped. Her thyroid stimulating hormone (TSH) was 0.007 uIU/mL (range: 0.4-4 uIU/mL), free thyroxin (fT4) was 3.43 ng/dl (range: 0.8-1.9 ng/dl) and free triiodothyronin (fT3) was 3.88

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pg/ml (range: 1.57-5.3). Propylthiouracil-induced antineutrophil cytoplasmic antibody-positive (ANCA(+)) panniculitis was diagnosed based on biopsy and laboratory findings. Systemic steroid therapy (methylprednisolone 40 mg daily) was started. On the 7th day of therapy, signs and symptoms of hyperthyroidism recurred (TSH: 0.005 uIU/mL, fT4: 7.77 ng/dl, fT3: 9.49 pg/ml) and serum thyroid hormone concentrations progressively increased. TSH receptor antibodies, thyroglobulin antibodies and thyroid peroxidase antibodies were all negative. Ultrasonographic examination revealed diffuse enlargement of the thyroid gland including the right lobe with retrosternal extension. There were so many nodules with the biggest one 28x30mm in size, localized in the right lobe. Thyroid scintigraphy with 99m technetium showed a heterogeneous patchy uptake on the gland, a hyperactive nodule in the right lobe with a hypoactive component as well as hypoactive and hyperactive nodules in the left lobe. The diagnosis was TMNG and surgery was planned. In order to prepare the patient for surgery, methimazole 40 mg daily was started. However, after 3 weeks, she presented to another clinic with fatigue and nausea. Her biochemical parameters were as follows: TSH: 0.005 uIU/mL, fT4: 7.77 ng/dl, fT3: 24.55 pg/ml, neutrophil count: 1370/µL. Methimazole was stopped for the mild neutropenia and Lugol's solution was added to the regimen. But normalization of the fT4 and fT3 levels could not be achieved.

After that, she applied to our institution of her own volition for the rest of her treatment. Her physical examination was unremarkable except for the healing dermal lesions on the bilateral lower extremities. Thyroid function tests revealed fT3 (17 pg/ml) and fT4 (>7 ng/dl) levels higher than normal levels along with suppressed TSH level (<0.01 uIU/mL). Her hematologic and biochemical parameters were all normal, thus, in order to achieve euthyroidism, methimazole at a dose of 40 mg daily was started along with β-receptor antagonist therapy. Despite increasing the dose to 60 mg daily, euthyroidism could not be achieved on the 15th day. Therefore, plasmapheresis was decided for rapid preparation for surgery. The patient had 7 sessions of plasmapheresis. Plasmapheresis was performed with plasma exchange method by PlasautoΣ, Asahi Kasei, Japan. The replacement fluid was 10 fresh frozen plasma for each session (totally 2000 cc). Heparin was used as anticoagulant. The exchange volume was 1.5 L for each session. Each treatment lasted for 1.5 hours. All procedures were uneventful. Although thyroid hormone levels only moderately decreased, the patient was asymptomatic (Table 1). The patient underwent surgery with β-blocker and dexamethasone treatment.

## Discussion

TMNG is the second most common cause of hyperthyroidism. The thyroid gland has autonomously functioning nodules that secrete thyroid hormones. But in middle-aged and elderly people with a long-standing goiter and in areas of endemic iodine deficiency, it is the most common cause. With regard to therapy, antithyroid drugs, such as PTU and methimazole can block new hormone synthesis. PTU also inhibits the peripheral conversion of T4 to T3 and incorporation of iodine into thyroglobulin molecule. The main goal of the drug therapy is to make the patient euthyroid before radioactive iodine treatment or surgical intervention. Unfortunately, common adverse effects including agranulocytosis, hepatotoxicity, skin rashes or arthralgia/arthritis can hinder the usage of these agents (6). ANCA-positive vasculitis has been reported in association with PTU use. There is also a possible association between methimazole and ANCA-positive vasculitis, but the number of cases is too small to establish a cause-and-effect relationship (7). In the literature, there is only one case report about PTU-induced ANCA(+) panniculitis. The mechanism of this association is not clear yet (8).

Surgery is associated with significant perioperative mortality in patients with uncontrolled thyrotoxicosis mainly due to precipitation of thyroid storm. The conventional preoperative preparation for surgery other than antithyroid drugs includes β-blockers, steroids and plasmapheresis (9,10,11). Iodine administration should not be used as there is no increased hypervascularity in the gland and also, as there is a great risk of exacerbation of hyperthyroidism in TMNG (12,13).

In our case, the patient was on antithyroid treatment for over 6 years but medical treatment failed to control the thyroid hormone levels. Besides, side effects of the antithyroid drugs, such as mild neutropenia and panniculitis had limited the therapy for a few months. She had a large goiter with retrosternal extension and multiple nodules of varying sizes. Also, addition of Lugol's solution to the therapy resulted in exacerbation of thyrotoxicosis and increase in free thyroid hormone levels due to autonomously functioning nodules. Therefore, surgery was the only chance of an effective therapy. For the rapid preparation of the patient for surgery, plasmapheresis was done.

**Table 1. Values of circulating thyroid hormones observed before and after the plasmapheresis**

| | **fT3 (range=1.57-5.3pg/ml)** | **fT4 (range=0.8-1.9ng/dl)** | **TSH (range=0.4-4 uIU/mL)** |
|---|---|---|---|
| At admission | 17 | >7 | <0.01 |
| After conventional therapy | 15.4 | >7 | <0.01 |
| After 1st plasmapheresis | 7.72 | 5.67 | 0.01 |
| After 2nd plasmapheresis | 8.85 | >7 | 0.01 |
| After 3rd plasmapheresis | 8.62 | 6.7 | 0.02 |
| After 5th plasmapheresis | 6.87 | 5.34 | 0.02 |
| After 7th plasmapheresis | 6.95 | 5.46 | 0.02 |

Plasmapheresis is a therapeutic procedure in which plasma is extracted from the components of blood and instead of patient plasma, a colloid replacement solution (albumin and/or plasma) is infused. It is successfully used in the treatment of hyperthyroidism in selected patients who need more rapid hormonal control and develop complications associated with antithyroid drugs (14).

All thyroid hormones are bound to plasma proteins. The half-life in plasma is 5 days for thyroxine binding globulin, 1-2 days for transthyretin and 13 days for serum albumin (15). Thus, protein bound thyroid hormones are good candidates for removal by plasmapheresis. Displacement of thyroid hormones from the intra-cellular part into the replacement solution decreases concentrations of free thyroid hormones and is responsible for the therapeutic effectiveness (16). Plasma or human albumin solutions used for replacement also provide new binding sites for circulating free hormones. At least 1-1.5 times of plasma volume should be changed with plasma or human albumin for the effective procedure. However, this effect is usually transient and thyroid hormone levels increase within few days after plasmapheresis. (17,18,19,20).

We performed seven sessions of plasmapheresis. In the literature, number of plasmapheresis sessions done were usually less than or equal to 3 except a case of Jod Basedow with 17 sessions (21). Long standing and extremely enlarged multinodular goiter and previously used iodine had increased the thyroid hormone levels and this may be a cause of resistance to plasmapheresis. We observed a moderate decrease in fT3 (55%) and at least 22% decrease in fT4 levels after seven sessions. Although both fT3 and fT4 levels remained above the normal range, we did not observe any signs or symptoms of thyrotoxicosis or thyroid storm in the perioperative period. We continued to use the β-blocker and systemic steroid therapy in order to avoid thyroid storm during the operation and a few days after surgery.

Complications of plasmapheresis are hypotension, hemolysis, anaphylactic or allergic reactions, coagulopathy, vascular injury and infection (22). Coagulation proteins and, to some extent, platelets are also removed during plasmapheresis. These decreases may be important when removed plasma is replaced by colloidal solutions other than fresh frozen plasma. Fresh frozen plasma was used for the exchange and there was no complication of plasmapheresis in our case. Total thyroidectomy was performed successfully and pathological diagnosis of adenomatous nodular hyperplasia was established.

In conclusion, plasmapheresis can be considered a safe and effective alternative procedure to prepare patients for surgery when drug treatment fails or is contraindicated and when emergency surgery is required for patients with TMNG.

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