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Preoperative Therapeutic Plasmapheresis In Thyrotoxic Patients Who Did Not Effectively Treated With Antithyroid Drugs, Iodine And Corticosteroid

Anti-Tiroid İlaçlar, İyot ve Kortikosteroid Tedavinin Etkin Olmadığı Tirotoksik Hastalarda Preoperatif Plazmaferez Tedavisi

ABSTRACT

Introduction: Preoperative treatment options in thyrotoxic patients are antithyroid drugs, potassium iodide, beta blockers and corticosteroids. Sometimes these treatment regimens have not been so successful for the patients to make them ready for the operation. So we thought that plasmapheresis (PP) could be an alternative to these treatments.

Methods: Two thyrotoxic patients with Graves' disease and one patient with toxic multinodular goiter were included in the study. All patients were candidates to surgical operation due to the contraindication of other medical treatment choices. On admission, all patients had severe uncontrolled hyperthyroidism. In order to prepare our patients to operation, all the patients were given beta blockers and inorganic potassium iodide and corticosteroid at first but disease control could not be achieved in terms of thyrotoxicosis. So PP was performed at an average of 3 to 5 sessions.

Results: After PP, all patients' thyroid hormone concentrations were significantly reduced. One patient had an anaphylactic reaction during 3th session of PP. Total thyroidectomy was performed to all patients without any complications.

Conclusions: We concluded that PP could be used as an alternative therapeutic option in the preoperative management of severe thyrotoxic patients.

Key words: Thyrotoxicosis, plasmapheresis, thyroid surgery

ÖZET

Giriş: Tirotoksik hastalarda preoperatif tedavi seçenekleri antitiroid ilaçlar, potasyum iyodür, beta blokerler ve kortikosteroidlerdir. Ancak zaman zaman bu tedavi modaliteleri hastaya ötiroid hale getirmekte yetersiz kalabilmektedir. Böyle durumlarda plazmaferez uygulaması alternatif bir tedavi yöntemi olarak hatırlanmalıdır.

Metod: Üç tirotoksik hasta bu çalışmaya dahil edildi. Hastaların ikisine Graves Hastalığı birine ise toksik multinodüler guatr tanısı konulmuştu. Hastaların hepsinde diğer medikal tedavi seçenekleri kontrendike olması nedeniyle cerrahi tedavi tercih edildi. Başvuru sırasında bütün hastaların kontrol altına alınamayan ciddi hipertiroidizmi mevcuttu. Bu nedenle hastaları operasyona hazırlayabilmek için bütün hastalara beta bloker, inorganic potasyum iyodür, ve kortikosteroid tedavisi başlandı ancak hastalarda ötiroidizm sağlanamadı bunun üzerine hastalara ortalama 3-5 seans plazmaferez uygulandı.

Sonuçlar: Plazmaferez sonrası hastaların hepsinde tiroid hormon konsantrasyonları anlamlı olarak azaldı. Bir hastada 3. seans sırasında anafaktik reaksiyon gelişti. Hastaların hepsinde total tiroidektomi başarılı bir şekilde uygulandı ve hiçbir komplikasyon gelişmedi.

Tartışma: Plazmaferez ciddi tirotoksik hastaları operasyona hazırlama aşamasında diğer tedavi seçeneklerine alternatif bir yöntemdir.

Anahtar kelimeler: tirotoksikoz ,plazmaferez, tiroid cerrahisi

INTRODUCTION

Thyrotoxicosis refers to any condition characterized by excess of circulating thyroid hormones mainly due to toxic multinodular goitre (TMNG) and Graves' Disease (GD) leading to multisystem involvement with a high mortality rate (1). The goals of treatment for thyrotoxicosis are to control symptoms efficiently and restore euthyroidism. Antithyroid drugs, radioiodine treatment and surgery all effectively restore euthyroidism, but have potentially serious side effects.

Plasmapheresis (PP) primarily removes protein-bound solutes or high-molecular weight solutes such as circulating protein-bound toxins, autoantibodies, immune complexes, or other abnormally occurring molecules (2). It has been used in the treatment of more than 100 diseases in human medicine, including immune-mediated diseases, neoplasm, infectious diseases, sepsis, hyperlipidemia, thyrotoxicosis, and removal of toxins (3).

PP is not often used in the treatment of thyrotoxicosis. It can be an alternative method in the preoperative care of patients with thyrotoxicosis (4-6). PP was first utilized in the treatment of hyperthyroidism in the 1970s with a further delineation of its use being described in the treatment of thyroid storm or thyroid hormone overdose in 1985 (7). Therapeutic PP in patients with severe hyperthyroidism was applied in whom antithyroid drugs are contraindicated. Thyroid hormones are almost entirely (>99%) bound to plasma proteins which could be effectively removed by PP (8). In the case of concomitant disorders, preoperative antithyroid drug intolerance/resistance or other insufficient treatment options, PP is an alternative and effective therapeutic tool.

We herein reported three thyrotoxic patients with GD and TMNG whom were prepared to thyroid operation by PP preoperatively.

MATERIAL AND METHODS

Two thyrotoxic patients with Graves' disease and one patient with toxic multinodular goiter were included in the study. Thyrotoxicosis was confirmed in all patients by the presence of decreased levels of serum thyrotropin (TSH), and increased levels of free T3 (FT3) and free T4 (FT4). Commercially available kits were used to determine the serum concentrations of FT4 and FT3. TSH, FT3 and FT4 levels were evaluated using the Abbott Architect 2000 device and Chemiluminescent Microparticle Immunoassay (CMIA) method. All patients' ultrasonographic examination was performed by the same endocrinologist. We performed the PP procedure in our three patients following the initial evaluation.

During the PP procedure, the removed plasma was replaced by fresh-frozen plasma. PP was performed using a continuous flow cell separator, ASTEC 204 (Fresenius, Germany). The total removed plasma volume was 7,500 ml (2,500 ml/session). Replacement fluids were consisted of fresh-frozen plasma (50 ml/kg).

FINDINGS

The patients' demographic and clinical characteristics are presented in table 1. All patients were treated by a regimen of saturated solution of potassium iodide, corticosteroids (40 mg/daily) and beta blockers, but it

was impossible to reach to the target hormone levels before the operation with that treatment. Because of this, we decided to perform PP as explained before. After PP, all patients had become euthyroid before they underwent to thyroid operations.

Patient 1

A 30-years-old woman was admitted to our department with severe hyperthyroidism due to GD. On admission, thyroid stimulating hormone (TSH) level was 0.01 μ U/ml (0.35-4.94), FT3 was 17.79 pg/ml (1.71-3.71) and FT4 was 3.64 ng/dl (0.70-1.48). Propylthiouracil (PTU) (300 mg/day) and propranolol (80 mg/day) were instituted as the initial treatment. Because of the development of drug-induced hepatotoxicity, propylthiouracil was changed to methimazole (60 mg/day). In the follow up, severe drug-induced urticaria occurred, so methimazole was also stopped. We planned radioactive iodine treatment; however she did not accept it. Thyroid surgery was planned to restore euthyroidism. Before the operation, saturated solution of potassium iodide was added to a regimen of corticosteroids (40 mg/daily) and beta blockers. However, on the 7th day of treatment, her thyroid hormone concentrations were still too high for the operation (Table 1). Therapeutic PP was applied for four sessions. After the fourth session, FT3 concentration was 3.95pg/ml and FT4 was 1.49ng/dl. Twenty-four hours after the last PP session, the patient underwent thyroid surgery. Near-total thyroidectomy was performed successfully.

Patient 2

A 50-years-old woman was admitted to our clinic with severe thyrotoxicosis symptoms of tremor, tachycardia and dyspnea. Physical examination revealed arrhythmia in cardiac examination and stridor in pulmonary examination. She has been using PTU (600 mg/day) for 3 months with a diagnosis of TMNG, but TSH level was still depressed and FT3 and FT4 levels were very high as shown in table 1. We planned to operate the patient with a diagnosis of TMNG that was also causing a severe tracheal compression. We added a saturated solution of potassium iodide, propranolol and corticosteroid to her therapy regimen, but thyroid hormone concentrations still remained too high for the operation at the sixth day of this treatment. In order to remove the thyroid hormones from the circulation rapidly for better hormonal control, PP was performed for five sessions. After 5 consecutive PP sessions, thyroid hormone levels were significantly decreased (Table 1). After that, she was operated successfully without any problems.

Patient 3

A 26-years-old man with GD was admitted to our

clinic that had been treated with PTU (900 mg/day) and propranolol for 2 years. Although he has taken a long term treatment with maximum doses, he was still thyrotoxic (Table 1). On physical examination he had grade 4 ophthalmopathy and tachycardia. Total thyroidectomy was planned and saturated solution of potassium iodide and corticosteroid (40 mg/day) treatment was added to his therapy regimen for the consecutive 6 days. After all these treatment interventions, he was still thyrotoxic, so we decided to perform 3 sessions of PP. On the 3rd session of PP, he had an anaphylactic reaction to plasma exchange, so the session was stopped. After 3rd session of PP, thyroid hormone levels were reduced as shown in table 1. He was operated successfully without any complications.

DISCUSSION

Thyrotoxicosis refers to any condition characterized by excess of circulating thyroid hormones leading to multisystem involvement with a high mortality rate (1). GD is the most common cause of thyrotoxicosis that is characterized by toxic diffuse goitre, ophthalmopathy and localized dermopathy (9). TMNG is the second most common cause of hyperthyroidism after GD (10).

The ideal treatment for GD and TMNG consists of antithyroid drugs, radioactive iodine, and surgery (9). In TMNG and GD, the main goal of this therapy is to bring the patient into euthyroid state before radioactive iodine treatment or surgical intervention (10). Surgery is associated with significant postoperative mortality in patients with uncontrolled thyrotoxicosis, mainly due to precipitation of thyroid

storm (11).

Preoperative uncontrolled thyrotoxicosis is a potentially life-threatening condition than can be associated with significant postoperative mortality. Because of this, euthyroidism must be substituted by several medical interventions before surgery. Thionamides are the preferred initial treatment unless contraindicated, but do require several weeks to render a patient euthyroid. Beta-blockers should always be used unless absolutely contraindicated because they improve thyrotoxic symptoms. Other agents including iodine and steroids can be used if rapid preparation is required or more severe thyrotoxicosis is present (11). Baeza et al. reported that with the use of betamethasone, iopanoic acid and propranolol for 5 days, thyroidectomy could be performed successfully on 6 of 14 patients in whom antithyroid drugs failed to control hyperthyroidism or coexisted with other medical conditions (12). Iopanoic acid alone, lithium alone, or high dose beta blocker alone are also used for preoperative preparation (4), but postoperative thyroid storm is reported to occur after preparation with lithium alone (13). Furthermore, it is reported that patients treated with beta blockers alone experienced more postoperative problems (e.g., fever, tachycardia) (14). Although PP has been used mainly for the treatment of thyroid storm, it could be preferred for the prevention of thyroid storm in selected patients whose thyroid hormone concentrations could not be decreased to safer levels using medical treatment strategies such as iopanoic acid, lithium, beta blockers or their combinations (6).

	Variable	Normal Range	On Admission	Before plasmapheresis (after other treatments)*	After plasmapheresis
Patient 1 F/30 years old	TSH (μ U/mL)	0,35-4,94	0,01	0,01	0,01
	FT4 (ng/dl)	0,7-1,48	3,64	3,4	1,49
	FT3 (pg/ml)	1,71-3,71	17,79	15,5	3,95
Patient 2 F/50 years old	TSH (μ U/mL)	0,35-4,94	0,01	0,17	0,19
	FT4 (ng/dl)	0,7-1,48	4,7	3,25	1,77
	FT3 (pg/ml)	1,71-3,71	30,09	7,02	3,81
Patient 3 M/26 years old	TSH (μ U/mL)	0,35-4,94	0,01	0,01	0,24
	FT4(ng/dl)	0,7-1,48	3,99	2,71	1,89
	FT3 (pg/ml)	1,71-3,71	19,74	12,27	3,29

* Other treatments: Saturated solution of potassium iodide, corticosteroid and beta blockers

Table 1. Characteristics of patients' hormone levels before and after plasmapheresis

Thyroid hormones are almost entirely (>99%) bound to plasma proteins which could be effectively removed by PP. The disappearance half-life in plasma is 5 days for thyroxine binding globulin, 1-2 days for transthyretin and 13 days for serum albumin (8). It is reported that after removal of protein-bound fractions of thyroid hormones from circulation, displacement of thyroid hormones from the cellular part is responsible for therapeutic effectiveness (15). Therefore thyroid hormones are good candidates for removal by PP. Free thyroid hormone concentrations may also decrease. Possible mechanisms for the decreases in free thyroid hormones could be the redistribution and dilution of thyroid hormones from intracellular part into the replacement fluids. In addition, if fresh-frozen plasma and/or human albumin are used for volume replacement, new binding sites will be available for circulating free hormones. This may also contribute to decreases in free hormone concentrations (6). Because of this; PP has been used successfully to treat severely hyperthyroid patients in distressed clinical situations. The use of PP, either solely or in combination with conventional therapies, may have a role in the treatment of patients with GD and TMNG. Although PP is rarely used in the routine treatment of thyrotoxicosis, it is an efficient method in the preoperative care of patients with thyrotoxicosis (6). Ozbey et al. reported that 4 GD patients were treated successfully before thyroid operation by PP (7). Schingler et al. treated 8 thyrotoxic patients by PP before thyroid operation. In both studies, they did not report any complications. Lukomskii et al. showed the efficacy of PP in preoperative management of 73 thyrotoxic patients who all were intolerant and resistant to thyrotoxic agents (16). Ezer et al. also reported 11 thyrotoxic patients treated effectively by PP. Although both fT3 and fT4 levels remained above the normal limits in two of 11 patients, the sign and symptoms of thyrotoxicosis improved in all patients and no thyroid storm observed during perioperative period (17).

PP is a relatively safe method with a mortality rate of 0.03-0.05%. Reported complications, which include citrate-induced paresthesias, muscle cramps and urticaria are all quite uncommon (18). Our third patient had an anaphylactic reaction during the third session of PP. Plasma exchange therapy requires central venous cannulation and carries the risk for transfusion, and costs of each PP sessions are considerable (19).

In conclusion, PP could be used as an alternative therapeutic option in the management of severely thyrotoxic patients to prepare them for surgery,

especially in patients who would need more rapid hormonal control and when other antithyroid therapies are ineffective or contraindicated.

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