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Effect of Plasma Exchange in Thyroid Storm With Consideration of Its Distribution Into the Extravascular Space

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Plasma exchange (PE), which directly removes some plasma thyroid hormones, is a treatment option for thyroid storm. However, the effect of PE has not been accurately assessed yet. Here we assessed the effect of PE in a patient with thyroid storm while taking into consideration the distribution of thyroid hormones in the extravascular space. A 51-year-old woman with thyroid storm underwent 2 PE procedures at our hospital. By measuring changes in thyroid hormone levels in plasma, fresh frozen plasma (FFP) used, and waste fluid during each 2.5-hour PE procedure, we calculated the efficiency of thyroid hormone removal based on the hypothesis that total thyroid hormone content before and after PE is the same. During the patient's first PE procedure, the estimated thyroxine (T_4) balance in the extravascular space (ΔX) was −70 μg, which corresponds to approximately 19% of T4 in the waste fluid. During the second PE procedure, ΔX was −131 μg, which corresponds to approximately 52% of T4 in the waste fluid. These data indicated that the source of removed T4 during PE varies. The amount of T_4 removed from the extravascular space should be taken into account during assessment of the effect of PE in thyroid storm.

Key Words: Graves disease, thyroid storm, plasma exchange, extravascular space

Thyroid storm is the state in which increased thyroid hormone levels reach critical levels. Plasma exchange (PE), which reduces circulating thyroid hormone levels, has been used as a treatment option for thyroid storm [1–4]. While thionamides take a relatively long time to suppress thyroid hormone synthesis, PE rapidly reduces plasma thyroid hormone levels, making it a theoretically useful therapy for patients with thyroid storm. However, to date, there have been only a few studies assessing the effect of PE, with varying results [2–4]. One reason could be that these previous studies assessed the effect of PE without consideration of the distribution of thyroid hormones in the extravascular space [5]. When the effect of thyroid hormone distribution in the extravascular space is taken into account, whole-body changes in thyroid hormone content during PE cannot be accurately assessed. Thus, in this study, we investigated the therapeutic effects of PE with consideration of thyroid hormone levels in the extravascular space by measuring the changes in thyroid hormone, thyroid-binding globulin

Abbreviations: FFP, fresh frozen plasma; PE, plasma exchange; PV, plasma volume; T3, triiodothyronine; T4, thyroxine; TBG, thyroid-binding globulin; TRAb, thyrotropin receptor antibody; ΔX, balance in the extravascular space.

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(TBG), anti-thyrotropin receptor antibody (TRAb) in plasma, amount of fresh frozen plasma (FFP) required, and volume of waste fluid produced during PE.

1. Patient and Methods

A. Clinical Course of a Patient With Graves Disease

A 51-year-old woman with a 5-year history of Graves disease was being treated with methimazole. During hospitalization for a left femoral trochanteric fracture at another hospital, she developed asymptomatic agranulocytosis (white blood cell count 1,100/µL; neutrophil count 286/µL). Methimazole was discontinued and inorganic iodine therapy was initiated. During rehabilitation 3 months after surgery for the fracture, she remained euthyroid with a small dose of inorganic iodine. She was scheduled for radical treatment for Graves disease after rehabilitation for the fracture. However, she suddenly complained of palpitations, diarrhea, and fatigue with elevated fever, which were suspected to be manifestations of thyrotoxicosis. Thus, she was transferred to our hospital for further treatment. Her height was 146.9 cm and her weight was 34.5 kg. She had a large goiter (estimated thyroid volume measured by ultrasonography was 104.1 cm^3). She had sinus tachycardia (heart rate 110/minute), high fever (38.0°C), and complained of diarrhea. Laboratory data showed thyrotoxicosis (thyrotropin <0.01 µIU/L; free triiodothyronine [free T_3] >32.6 pg/mL; free thyroxine [free T_4], >7.8 ng/dL), positive thyroid autoantibodies (thyroid peroxidase antibodies >600 IU/mL; thyroglobulin antibodies 526 IU/mL), and presence of TRAb (104.8 IU/L; Table 1). Imaging studies did not suggest the presence of heart failure. In accordance with Japan Thyroid Association criteria [6], thyroid storm was suspected. Thus, hydrocortisone (400 mg/day), potassium iodine (200 mg/day), and landiolol as needed were initiated (Fig. 1). On hospital day 4, based on our judgment that the treatment effect was inadequate, we increased the dosage of potassium iodine, replaced the short-acting steroid with a longer-acting steroid to more effectively block the conversion of T_4 to T_3, and added lithium carbonate (600 mg/day) to suppress hormone secretion. However, the patient responded

Table 1. Blood Testing Results

CBC			Reference				Reference
WBC count	3200	/µL	3600–8900	Uric acid	6.9	mg/dL	2.3–6.0
Neutrophil	57.4	%	2–90	Total cholesterol	79	mg/dL	150–219
Lymphocyte	34.8	%	25–48	Triglyceride	69	mg/dL	30–149
Monocyte	7.2	%	2–12	LDL cholesterol	32	mg/dL	70–139
Eosinophil	0.3	%	1–9	Sodium	141	mmol/L	135–145
Basophil	0.3	%	0–2	Potassium	3.3	mmol/L	3.5–5.0
RBC count	416	$\times 10^4$/µL	380–504	Chloride	104	mmol/L	96–107
Hemoglobin	11.1	g/dL	11.1–15.2	Calcium	9.0	mg/dL	8.8–10.6
Platelet count	20.2	$\times 10^4$/µL	15.3–34.6	Phosphate	4.5	mg/dL	2.4–4.5
Chemical				BNP	151.2	pg/mL	0.0–18.4
ALP	302	U/L	110–348	CRP	0.12	ng/mL	<0.30
AST	36	U/L	5–37	**Thyroid**			
ALT	43	U/L	6–43	TSH	<0.01	µIU/mL	0.56–4.3
LDH	203	U/L	119–221	Free T_3	>32.6	pg/mL	2.4–4.5
Creatine kinase	47	U/L	47–200	Free T_4	>7.8	ng/dL	1.0–1.7
Total protein	5.8	g/dl	6.5–8.5	TRAb	104.8	IU/L	<2.0
Albumin	3.1	g/dl	4.0–5.2	TPOAb	>600	IU/mL	<16
Blood urea nitrogen	23	mg/dl	9–21	TgAb	526	IU/mL	<28
Creatinine	0.29	mg/dl	0.50–0.80	Thyroglobulin	1060	ng/mL	<33.6

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain-type natriuretic peptide; CRP, C-reactive protein; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; RBC, red blood cell; TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T^4, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TRAb, anti-thyrotropin receptor antibody; WBC, white blood cell.

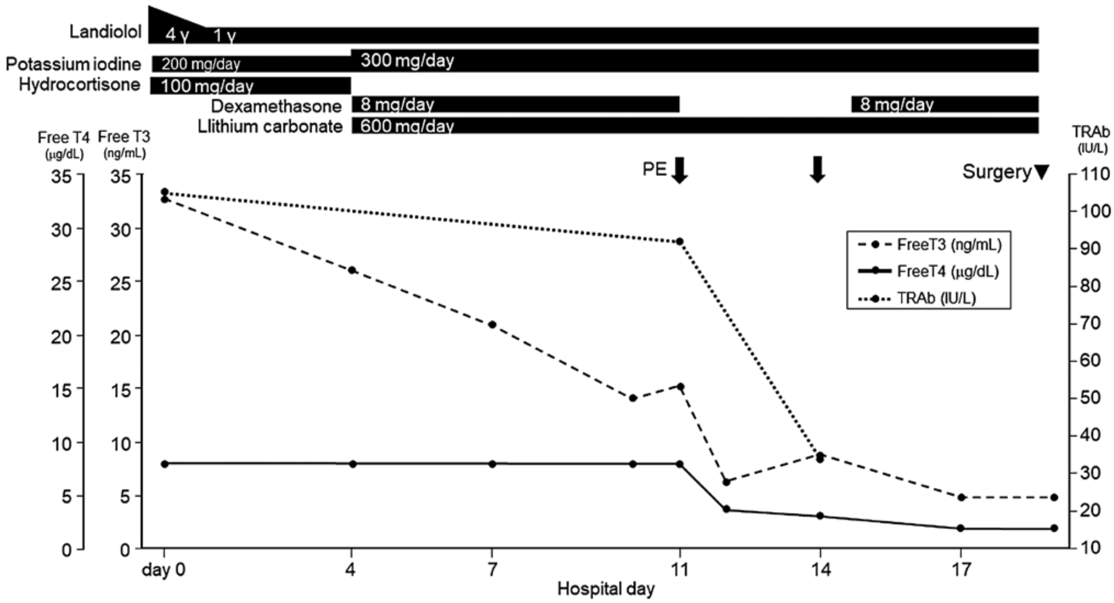

Figure 1. Clinical Course of Thyrotoxicosis. Plasma exchange was performed on hospital days 11 and 14. Surgery was performed on hospital day 19. The over-limit data of free triiodothyronine ([T3] >32.6 pg/mL) on day 0 (admission) and free thyroxine ([T4] >7.8 pg/mL) from day 0 to day 11 (at the beginning of plasma exchange [PE]) were assigned as upper-limit values. Landiolol 1γ = 1 μg/kg/min. Abbreviations: TRAb, thyrotropin receptor antibody; y, year.

poorly to treatment that would allow for surgery to be performed safely, so we decided to perform PE before surgery based on 2016 American Thyroid Association guidelines [7].

B. Plasma Exchange

The patient underwent 2 PE procedures. Each PE procedure entailed exchanges of approximately 2900 mL of FFP as replacement solution over approximately 2.5 hours. Both procedures involved single-filtration PE using nafamostat mesylate for anticoagulation and a blood access catheter kit for vascular access.

C. Specimen Sampling

We took blood samples at the beginning of PE, 10, 15, 30, 60, 90, 120, and 150 minutes after the start of PE and at the end of PE. We also took a sample from each bag of FFP (Japan Red Cross Society) and a sample of a part of total waste plasma. For all specimens, we measured T_3 and T_4 concentrations and TRAb titers. We used a commercial electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics, Tokyo) to measure total T_3 and T_4 concentrations (normal range for T_4: 6.18–12.40 μg/dL; for T_3: 0.80–1.60 ng/mL). We used the ECLusys TRAb 2-step radioreceptor assay (Roche Diagnostics) to measure TRAb titers (normal range <2.0 IU/L; detectable level ≥0.3 IU/L). We also measured serum free T_4 and free T_3 concentrations using ECLIA (Roche Diagnostics) to assess the patient's clinical condition. (For these assays, the reference range is 1.00–1.70 ng/dL for free T_4 and 2.40–4.50 pg/mL for free T_3.)

D. Estimation of Whole-Body Plasma Volume

In this study, we used Gibson's formula [8, 9] to calculate circulating plasma volume (PV) by multiplying average circulating plasma volume per area of body surface for this patient (2715 mL/m^2) by hematocrit, as follows:

$$\text{Whole-body plasma volume (PV)} = 2715 \times [\text{height (1.469 m)}^{0.725} \times \text{body weight (kg)}^{0.425} \times 0.007184] \times (1 - \text{hematocrit [\%]}/100)$$

E. Calculation of Amount of Thyroid Hormone

We calculated thyroid hormone balance during PE with an assumption of equality as follows:

$$\text{Before PE [(whole-body thyroid hormone content : plasma [preP] + extravascular space [preX]) + FFP] = After PE [(whole-body thyroid hormone concentration : plasma [postP] + extravascular space [postX]) + waste fluid]}$$

Using this equation, the change in thyroid hormone content in the extravascular space was calculated as follows:

$$(\text{postX} - \text{preX}) = [(\text{preP} - \text{postP}) + \text{FFP} - \text{waste fluid}]$$

2. Results

For the first PE procedure, the estimated PV was 1.54 L before the procedure and 1.57 L after the procedure. For the second PE procedure, the values were 1.48 L and 1.50 L, respectively. The difference between PV before and after PE was small (0.02–0.03 L). Figure 2 shows the changes in estimated plasma thyroid hormone content during PE. During the first PE

min	0	10	15	30	60	90	120	150	End
BW (kg)	32.4								32.7
Hct (%)	37.1								37.0
T3 (μg)	9.8	9.3	9.1	9.5	9.4	8.9	9.2	8.9	8.9
T4 (μg)	644	509	482	455	405	395	381	388	425

min	0	10	15	30	60	90	120	150	End
BW (kg)	29.6								30.0
Hct (%)	36.6								36.7
T3 (μg)	8.0	8.1	8.1	7.9	8.1	8.1	8.5	7.3	9.0
T4 (μg)	342	281	279	273	271	275	286	253	312

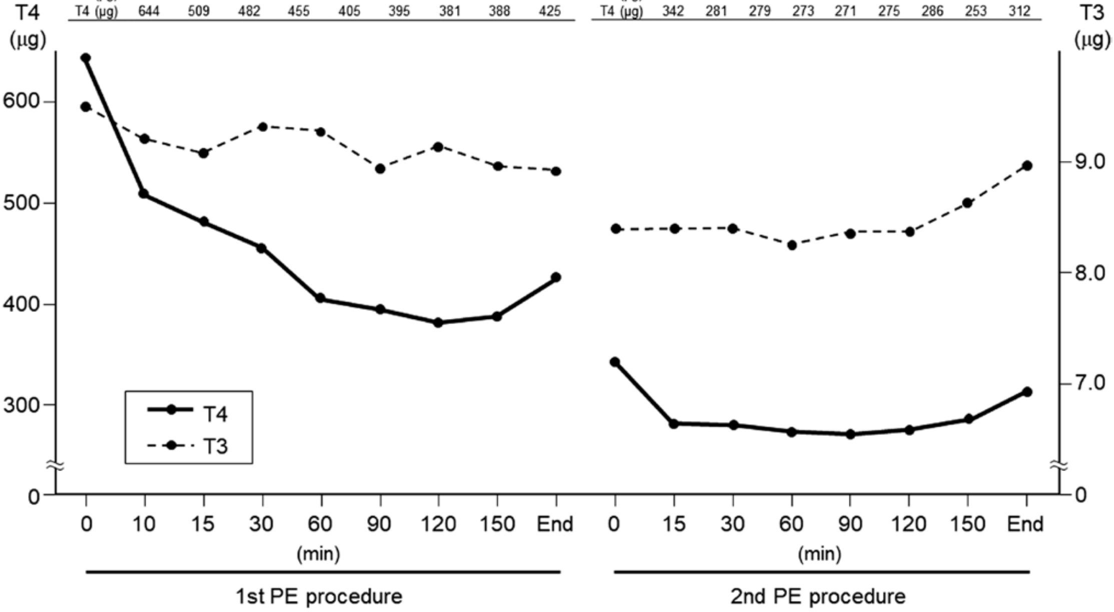

Figure 2. Changes in Plasma Triiodothyronine and Thyroxine Content During Plasma Exchange (PE). Estimated plasma triiodothyronine (T_3) and thyroxine (T_4) content over time during the first and second PE procedures. The interval between the first and second PE procedures was 3 days. Abbreviations: BW, body weight; Htc, hematocrit.

procedure, plasma content of both T_4 and T_3 continuously decreased until 120 minutes after the beginning of PE. An absolute reduction in plasma T_3 and T_4 content was observed at the end of PE. The second PE procedure took place 3 days after the first PE procedure. Plasma thyroid hormone content at the beginning of the second PE procedure was much lower than content at the end of the first PE procedure. During the second PE procedure, decreases in plasma T_4 and T_3 content were not observed. T_3 and T_4 content were higher at the end of the second PE procedure despite a constant PE speed. These data suggest that the reduction in plasma thyroid hormones was not consistent during PE. Accordingly, we estimated the balance of T_4, TBG, and TRAb levels during PE using assumptions of equality.

Table 2 shows the content and estimated balance of T_4 and TBG during each PE procedure. For the first PE procedure, the estimated plasma content of T_4 was 644 µg and 426 µg before and after PE, respectively. T_4 content was 89 µg in total FFP and 337 µg in waste fluid. The estimated balance in the extravascular space (ΔX) was −70 µg, approximately 18.6% of T_4 content in the waste fluid. For the second PE procedure, ΔX was −131 µg, approximately 51.8% of T_4 content in the waste fluid. Faber et al found the rate of T_4 turnover was 36.7 nmol (28.5 µg)/day [10]. When corrected by PE duration (approximately 2.5 hours), the rate of T_4 turnover was assumed to be 3.0 µg. When the rate of T_4 turnover was taken into account, net ΔX for T_4 was −67 µg for the first PE procedure and −128 µg for the second PE procedure, which indicates that the movement of T_4 into waste fluid was much higher than T_4 turnover in plasma. T_4 movement into the extravascular space is a considerable contributor to T_4 removal during PE, and the distribution of T_4 sources during PE was not constant.

Of note, the estimated balance of TBG (ΔX) was −17.8 mg for the first PE procedure and −25.0 mg for the second PE procedure (Table 2). The estimated balance of plasma TRAb was −97 IU and −64 IU for the first and second PE procedures, respectively (Table 3).

At 1 day and 3 days after the first PE procedure, plasma free T_4 levels were 3.6 and 2.9 ng/dL, respectively (Fig. 1). Five days after the second PE procedure, the patient successfully underwent total thyroidectomy. The pathological features of the resected thyroid were consistent with Graves disease. Overall, PE seemed to be effective in improving her condition.

Table 2. Estimated Thyroxine and Thyroid-Binding Globulin Content in Plasma at the Beginning and End of Plasma Exchange, Total Fresh Frozen Plasma, and Waste Fluid

Parameter	PE procedure	Before PE	After PE	FFP	Waste fluid	ΔX
T_4 (µg)	1	644	426	89	377	−70
	2	342	312	92	253	−131
TBG (mg)	1	48.6	54.0	27.6	40.0	−17.8
	2	55.7	61.4	29.7	49.0	−25.0

FFP, fresh frozen plasma; PE, plasma exchange; T_4, thyroxine; TBG, thyroid-binding globulin; ΔX, estimated balance in the extravascular space.

Table 3. Estimated Thyrotropin Receptor Antibody Titers in Plasma at the Beginning and End of Plasma Exchange, Total Fresh Frozen Plasma, and waste Fluid

Parameter	PE procedure	Before PE	After PE	FFP	Waste fluid	ΔP
TRAb (IU)	1	310	77	0	97	-233
	2	111	42	0	64	-69

FFP, fresh frozen plasma; PE, plasma exchange; ΔP, estimated balance in the plasma; TRAb, thyrotropin receptor antibody.

3. Discussion

This is the first report to assess the effect of PE in patients with thyroid storm that takes whole-body balance of T_4 during PE into consideration. Here, we showed that PE was effective for removing T_4 in this patient, although the proportion of T_4 removed from various origins during PE was not constant.

Previous studies evaluating the effect of PE have demonstrated absolute changes in plasma thyroid hormone levels during PE. However, they concluded that a remarkable effect was not observed [2–4]. Those studies did not consider thyroid hormone content in the extravascular space. Indeed, the extravascular space is considered another location for T_4 and TBG [5]. To investigate the kinetics of T_4, Irvine and Simpson-Morgan monitored the appearance of T4 labeled with exogenous iodine (^{125}I-T_4) and albumin labeled with iodine 131 (^{131}I-albumin) over time, which bind to T_4 from central venous catheters in the hepatic, intestinal, and popliteal lymph ducts in sheep [11]. They found that exogenous ^{125}I-T_4 and ^{131}I-albumin in the vascular space flow into lymph ducts, and their distribution between the vascular and extravascular spaces (lymph ducts) reached an equilibrium. In addition, Fisher et al investigated the peripheral kinetics of T_4 labeled with iodine 131 (131I-T_4) in healthy adults and patients with thyrotoxicosis using a four-compartment mathematical model [12]. They found that total T_4 distribution in plasma, liver, and extravascular space (lymph ducts and interstitial tissue) is more extensive in patients with thyrotoxicosis than in healthy adults. Accordingly, our calculations for assessing the effect of PE seem reasonable.

Regarding the relationship between changes in plasma and extravascular space T_4 content, a large amount of T_4 wasting from plasma was accompanied by a small amount of T_4 wasting from the extravascular space during the first PE procedure, which might reflect a large reduction in plasma T_4 levels. Conversely, a small amount of T_4 wasting from plasma was accompanied by a large amount of T_4 wasting from the extravascular space during the second PE procedure, which might reflect a small reduction in the plasma T_4 (or free T_4) levels. We are not aware of the factors regulating the wasting fractions in each PE.

This study had several limitations. First, estimations of circulating PV and turnover rate were based on assumption of equality as in previous studies. Second, this case report is based on a single patient. We need further investigations involving patients with Graves disease who undergo PE to elucidate its true therapeutic effects.

In conclusion, we demonstrated that PE is effective for removing thyroid hormones. The true therapeutic effects of PE might have been misinterpreted when only changes in plasma concentrations of thyroid hormones were taken into account.

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Additional Information

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Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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