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 (T4) 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 T4 removed from the extravascular space should be taken into account during assessment of the effect of PE in thyroid storm.

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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
(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 cm³). 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 T₃] >32.6 pg/mL; free thyroxine [free T₄], >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 T₄ to T₃, 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      | 3600–8900 | Uric acid  |
| Neutrophil              | 57.4      | 2–90      | Total cholesterol  |
| Lymphocyte              | 34.8      | 25–48     | Triglyceride  |
| Monocyte                | 7.2       | 2–12      | LDL cholesterol  |
| Eosinophil              | 0.3       | 1–9       | Sodium  |
| Basophil                | 0.3       | 0–2       | Potassium  |
| RBC count               | 416 ×10⁶/µL | 380–504 | Chloride  |
| Hemoglobin              | 11.1      | 11.1–15.2 | Calcium  |
| Platelet count          | 20.2 ×10⁹/µL | 15.3–34.6 | Phosphate  |
| **Chemical**            |           |           |            |
| ALP                     | 302       | 110–348   | CRP  |
| AST                     | 36        | U/L       | 5–37       |
| ALT                     | 43        | U/L       | 6–43       |
| LDH                     | 203       | U/L       | 119–221    |
| Creatine kinase         | 47        | U/L       | 47–200     |
| Total protein           | 5.8       | g/dL      | 6.5–8.5    |
| Albumin                 | 3.1       | g/dL      | 4.0–5.2    |
| Blood urea nitrogen     | 23        | mg/dL     | 9–21       |
| Creatinine              | 0.29      | mg/dL     | 0.50–0.80  |

**Thyroid**

- BNP: 151.2 pg/mL (0.0–18.4)
- CRP: 0.12 mg/dL (<0.30)
- TSH: <0.01 µIU/mL (0.56–4.3)
- Free T₃: >32.6 pg/mL (2.4–4.5)
- Free T₄: >7.8 ng/dL (1.0–1.7)
- TRAb: 104.8 IU/L (<2.0)
- TPOAb: >600 IU/mL (<16)
- TgAb: 526 IU/mL (<28)
- 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; T₃, triiodothyronine; T₄, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TRAb, anti-thyrotropin receptor antibody; WBC, white blood cell.
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 T₃ and T₄ concentrations and TRAb titers. We used a commercial electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics, Tokyo) to measure total T₃ and T₄ concentrations (normal range for T₄: 6.18–12.40 μg/dL; for T₃: 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 T₄ and free T₃ 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 T₄ and 2.40–4.50 pg/mL for free T₃.)

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/m²) by hematocrit, as follows:

![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.](image-url)
Whole-body plasma volume (PV) = 2715 × [height (1.469 m)]^{0.725} × body weight (kg)^{0.425} × 0.007184 × (1 – hematocrit [%]/100)

E. Calculation of Amount of Thyroid Hormone

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

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:

(postX – preX) = [(preP – postP) + FFP – 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

![Figure 2](image-url)
procedure, plasma content of both T₄ and T₃ continuously decreased until 120 minutes after the beginning of PE. An absolute reduction in plasma T₄ and T₃ 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 T₄ and T₃ content were not observed. T₃ and T₄ 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 T₄, TBG, and TRAb levels during PE using assumptions of equality.

Table 2 shows the content and estimated balance of T₄ and TBG during each PE procedure. For the first PE procedure, the estimated plasma content of T₄ was 644 μg and 426 μg before and after PE, respectively. T₄ 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 T₄ content in the waste fluid. For the second PE procedure, ΔX was −131 μg, approximately 51.8% of T₄ content in the waste fluid. Faber et al. found the rate of T₄ turnover was 36.7 nmol (28.5 μg)/day [10]. When corrected by PE duration (approximately 2.5 hours), the rate of T₄ turnover was assumed to be 3.0 μg. When the rate of T₄ turnover was taken into account, net ΔX for T₄ was −67 μg for the first PE procedure and −128 μg for the second PE procedure, which indicates that the movement of T₄ into waste fluid was much higher than T₄ turnover in plasma. T₄ movement into the extravascular space is a considerable contributor to T₄ removal during PE, and the distribution of T₄ 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 T₄ 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.

| Parameter | PE procedure | Before PE | After PE | FFP | Waste fluid | ΔX |
|-----------|--------------|-----------|----------|-----|-------------|----|
| T₄ (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; T₄, thyroxine; TBG, thyroid-binding globulin; ΔX, estimated balance in the extravascular space.

| 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 T₄ during PE into consideration. Here, we showed that PE was effective for removing T₄ in this patient, although the proportion of T₄ 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 T₄ and TBG [5]. To investigate the kinetics of T₄, Irvine and Simpson-Morgan monitored the appearance of T₄ labeled with exogenous iodine (¹²⁵I-T₄) and albumin labeled with iodine 131 (¹³¹I-albumin) over time, which bind to T₄ from central venous catheters in the hepatic, intestinal, and popliteal lymph ducts in sheep [11]. They found that exogenous ¹²⁵I-T₄ and ¹³¹I-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 T₄ labeled with iodine 131 (¹³¹I-T₄) in healthy adults and patients with thyrotoxicosis using a four-compartment mathematical model [12]. They found that total T₄ 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 T₄ content, a large amount of T₄ wasting from plasma was accompanied by a small amount of T₄ wasting from the extravascular space during the first PE procedure, which might reflect a large reduction in plasma T₄ levels. Conversely, a small amount of T₄ wasting from plasma was accompanied by a large amount of T₄ wasting from the extravascular space during the second PE procedure, which might reflect a small reduction in the plasma T₄ (or free T₄) 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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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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