ORIGINAL RESEARCH—CLINICAL

Iodine-131 Combined With Plasma Exchange Treatment in Graves' Hyperthyroidism Patients With Severe Liver Injury Whose Average Model for End-Stage Liver Disease Scores >20

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BACKGROUND AND AIMS: The purpose of this retrospective study is to describe the Graves' hyperthyroidism patients with severe liver injury treated by iodine-131 combined with plasma exchange (PE). **METHODS:** The patients who had hyperthyroidism caused by Graves' disease, with severe liver injury (The level of total bilirubin $\geq$12 mg/dL), and after 1 week of liver protective medication treatment, the patient's liver function did not improve, were enrolled in this study. All patients were treated with iodine-131 and PE. The patients' laboratory data after 3 months of isotope therapy were collected. **RESULTS:** In this study, there were 8 patients included, the average model for end-stage liver disease (MELD) scores were greater than 20 (ranges from 19 to 30) at baseline. The levels of hemoglobin, platelet count, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, alkaline phosphatase, glutamyl transpeptidase, MELD scores, free triiodothyronine, free thyroxine, antithyroid peroxidase autoantibody and serum thyrotropin receptor antibodies after PE treatment were significantly lower than before PE treatment ($P < .05$). The level of total bilirubin at 3 months post-131I treatment was significantly lower than pre-131I treatment ($P = .0200$), the same was the level of direct bilirubin ($P = .0200$). **CONCLUSION:** Our study enrolled Graves' hyperthyroidism patients with severe liver injury whose average MELD scores were greater than 20, and shows that liver function test can recover on about 3 months treated iodine-131 combined with PE therapy.

Keywords: Graves' Disease; Isotope I131 Therapy; Plasma Exchange; Liver Failure

Introduction

Hyperthyroidism is characterized by increased thyroid hormone synthesis and secretion from the thyroid gland, and the most common cause of hyperthyroidism is Graves' disease (GD).[1] The prevalence of GD approximates 1%–1.5% in the population as a whole.[2] It is an autoimmune disease directly caused by circulating autoantibodies that bind to the thyrotropin receptor, subsequently increasing thyroid hormone production and release, proliferation of thyrocytes, and enlargement of the thyroid gland. Three equally potent approaches are offered to treat Graves' hyperthyroidism: antithyroid drugs (ATD) therapy by inhibiting production of thyroid hormones, complete surgical removal of the thyroid gland (total thyroidectomy), or radioactive iodine (RAI) induced shrinkage of the thyroid tissue.[3] Although abnormal liver enzymes are frequently seen in patients with thyrotoxicosis before treatment, liver failure, as a severe state of liver injury, are rarely seen. Hepatotoxicity occurs in 0.3% patients exposed to methimazole (MMI) and 0.15% of those given propylthiouracil.[2] Liver transaminase enzyme levels elevated more than 5-fold above the upper limit of normal should prompt serious reconsideration of initiating ATD therapy.[3] If the Graves' hyperthyroidism

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Abbreviations used in this paper: **ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATD, antithyroid drugs; ATG, antithyroglobulin antibodies; ATPO, antithyroid peroxidase autoantibody; CT, calcitonin; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; GGT, glutamyl transpeptidase; MELD, model for end-stage liver disease; MMI, methimazole; PE, plasma exchange; RAI, radioactive iodine; rT3, reverse triiodothyronine; TRAb, thyrotropin receptor antibodies; TT3, total triiodothyronine; TT4, total thyroxine; WBC, white blood cell count.**

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patients with severe liver injury, total thyroidectomy also may be a contraindication. Thus, RAI therapy may be the only option for them. There is still a lack of relevant data on the safety of RAI therapy in Graves' hyperthyroidism patients with severe liver injury.

If patients experience liver failure, they may require the extracorporeal removal of large compounds from the blood, including albumin-bound and water-soluble toxins and replacement with plasma. According to American Society for Apheresis guidelines 2023, acute liver failure is category I indication of high volume therapeutic plasma exchange (PE) with grade 1A recommendation, while it is category III indication of therapeutic PE with grade 2B recommendation.[4] PE treatment not only improves liver function, but also reduces thyroid hormone levels after iodine-131 treatment in Graves' hyperthyroidism patients with severe liver injury. However, more studies on iodine-131 combined with PE treatment in Graves' hyperthyroidism patients with severe liver injury are needed. The purpose of this retrospective study is to describe the Graves' hyperthyroidism patients with severe liver injury treated by iodine-131 combined with PE.

Patients and Methods

Patients and Study Cohort

This is a retrospective study including Graves' hyperthyroidism patients with severe liver injury treated with iodine-131 combined with PE at the Department of Infectious Diseases, Huashan Hospital, Shanghai medical college, Fudan University, Shanghai, China from March 2021 to March 2024. The Graves' hyperthyroidism was defined as the patients with following features: hypermetabolic symptoms and signs caused by increased sympathetic nervous system excitability, such as palpitations, excessive sweating, and irritability; diffuse thyroid enlargement; thyroid stimulating hormone levels decrease and FT4 levels increase; and serum thyrotropin receptor antibodies (TRAbs) positive.[3] The causes of abnormal liver function were major related to Graves' hyperthyroidism. For elevated bilirubin, cutoffs of 5–12 mg/dL have been examined in acute on chronic liver failure (Asian Pacific Association for the Study of the Liver/European Association for the Study of the Liver definitions).[5–7] Moreover, the patients with serum total bilirubin $\geq$12 mg/dL receive a highest liver score in the modified Sequential Organ Failure Assessment score.[8] Thus, the total bilirubin of patients with severe liver injury was defined as $\geq$12 mg/dL in this study. The patients with severe liver injury may not have coagulation dysfunction, so not all patients were liver failure patients. Inclusion criteria were as follows: patients had hyperthyroidism caused by GD; the total bilirubin of patients $\geq$12 mg/dL; after 1 week of liver protective medication treatment, the patient's liver function did not improve; the patients can have underlying liver disease, such as hepatitis B or C virus infection, or fatty liver disease, but liver function is normal before this onset. Exclusion criteria were as follows: patients aged less than 18 years old; patients infected with human immunodeficiency virus; patients during pregnancy or lactation; elevated bilirubin of patients before the onset of GD; patients not treated with PE; patients not treated with iodine-131. The patients' laboratory data after 3 months of isotope therapy were collected. All the patients or their representatives provided the written informed consent. The study was performed in accordance with the Helsinki Declaration and was approved by the Ethical Committee of Huashan Hospital, Fudan University (2024-679).

Clinical Characteristics

The clinical characteristics including age, gender, blood routing test, liver function, serum creatinine, international normalized ratio and thyroid function, were obtained from patients' medical records. All patients were evaluated by the model for end-stage liver disease (MELD) as a prognostic scoring system. MELD scores were calculated as follows: $9.6 \times \ln[\text{creatinine (mg/dL)}] + 3.8 \times \ln[\text{bilirubin (mg/dL)}] + 11.2 \times \ln(\text{international normalized ratio}) + 6.4$ (etiology: 0 if cholestatic or alcoholic, 1 otherwise). Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD scores calculation. If serum creatinine is >4.0 mg/dL, the data are treated as 4.0 for calculation.[9] The clinical characteristics of pre-PE treatment were collected at the day when the patients were received PE treatment, the clinical characteristics of post-PE treatment were collected at the next day after PE treatment. The clinical characteristics of pre-131I treatment were collected at the day when the patients were received iodine-131 treatment, the clinical characteristics of post-131I treatment were collected at the next day, 1 week, 1 month, and 3 months after iodine-131 treatment. If the patient experiences hypothyroidism during follow-up, levothyroxine sodium tablets should be used as a replacement therapy.

PE Treatment

PE was performed by centrifugal separation method on the hemocyte separator (FRESENIUS KABI COM.TEC, Germany) using blood preservation solution I (ACD-A, Shanghai Blood Biomedicine Co, Ltd, China) as our previous study.[10] The plasma volume exchanged in each procedure was 1.0 total plasma volume of the patient calculated according to body weight and hematocrit. 100% of replacement fluid was plasma for all procedures without albumin. The blood flow rate during the procedure was around 50 mL/min and was adjusted according to each patient's conditions. ACD-A was infused immediately in draw line port automatically with the whole blood to the ACD-A ratio of 14:1–16:1. Calcium gluconate (each 3 g diluted with 5% glucose solution 50 mL) was infused with 40–60 mL/h via return line, about 1.5 g calcium gluconate per liter exchanged plasma, about 3–5 g calcium gluconate for each procedure. For each procedure, peripheral vascular access was used by 2 superficial vein indwelling 18G needles (BD Intima II, Beckton Dickinson Medical, Franklin Lakes, NJ, USA) without using a central venous catheter or port, with the median cubital vein as draw line, and the superficial vein as return line. The needle was removed after each procedure. The number and frequency of PE procedures were decided based on both clinical assessment and the availability of plasma.

Iodine-131 Treatment

All patients with hyperthyroidism underwent 131I treatment at the Department of Nuclear Medicine & PET Center, Huashan Hospital. Thyroid ultrasonography, 99mTc Sodium Pertechnetate thyroid scintigraphy, and 131I uptake

measurements were employed to assess thyroid mass, dimensions, and iodine's effective half-life. Following consultations with multiple nuclear medicine specialists, personalized doses of 131I were calculated using the formula: therapeutic radioactivity (mCi) = (thyroid mass [in grams] × 131I activity [in μCi] per gram of thyroid tissue)/the 24-hour 131I uptake. A fixed dose of 131I (120 μCi per gram of thyroid tissue) was administered to all patients. Thyroid weight (in grams) was determined using SPECT imaging (GE Infinia II with Hawkeye Options). Subsequently, individualized doses were calculated based on each patient's thyroid weight.

Statistical Analysis

Statistical analyses were performed with the Graphpad 10.2.3 (Graphpad Software, San Diego, CA). Variables were expressed as mean ± standard deviation or median (range) unless otherwise specified. Differences in the parameters of 2 groups were compared using the unpaired parametric t-test, paired parametric t-test or nonparametric Mann-Whitney U test as needed. Differences in the parameters of multiple groups were compared using Kruskal-Wallis test. A 2-tailed P value of <0.05 was considered statistically significant.

Results

The Baseline Characteristics of Graves' Hyperthyroidism Patients with Severe Liver Injury

There were 8 patients included in this study, and all patients were Chinese. Baseline characteristics collected at the admission day and described in Table 1. Three patients had hepatic encephalopathy grade 1, the other patients were without hepatic encephalopathy. The level of total bilirubin in all patients were ≥12 mg/dL, and the average MELD scores were greater than 20 (ranges from 19 to 30) at baseline. Two patients had chronic hepatitis B and were treated by tenofovir; other patients didn't have any underlying diseases. Four patients had a history with MMI therapy and stopped MMI after admission. Figure 1 shows the treatment process diagram of the patients. The percentage of 131I uptake rate for 3 hours, 6 hours, and 24 hours was 56.1 ± 21.9, 67.33 ± 18.4, and 68.9 ± 22.9, respectively. All the patients used metoprolol (β-adrenergic blocking agent) to control hypermetabolic symptoms.

Table 1. Baseline Characteristics of Graves' Hyperthyroidism Patients With Severe Liver Injury

Characteristics	Value	Reference ranges
Age, y	33 (27–51)	NA
Male sex, n (%)	4 (50%)	NA
WBC ($\times10^9$/L)	6.3 ± 1.1	3.5–9.5
Hb (g/L)	114.6 ± 19.5	115.0–150.0
Platelet count ($\times10^9$/L)	201.9 ± 114.5	125.0–350.0
ALT (U/L)	38.0 (16.0–702.0)	7.0–40.0
AST (U/L)	54.0 (39.0–770.0)	13.0–35.0
Total bilirubin (μmol/L)	481.8 ± 202.0	≤21.0
Direct bilirubin (μmol/L)	332.3 ± 102.4	≤8.0
ALP (U/L)	155.1 ± 21.37	35.0–100.0
GGT (U/L)	52.0 (15.0–205.0)	7.0–45.0
Serum creatinine (μmol/L)	49.3 ± 19.0	57.0–97.0
INR	1.6 ± 0.5	0.9–1.2
MELD scores	23.2 ± 4.2	NA
TSH (mIU/L)	0.0 (0.0–0.3)	0.3–4.2
TT3 (nmol/L)	2.4 (1.6–10.0)	1.3–3.1
TT4 (nmol/L)	191.5 ± 96.6	66.0–181.0
FT3 (pmol/L)	9.7 (5.2–50.0)	3.1–6.8
FT4 (pmol/L)	53.8 ± 34.8	12.0–22.0
TG (ng/mL)	44.5 (0.8–500.0)	3.5–77.0
ATPO (IU/mL)	211.4 ± 227.2	<34.0
ATG (IU/mL)	22.9 (15.8–3169)	<115.0
TRAb (IU/L)	23.0 ± 13.5	<1.8
rT3 (nmol/L)	5.3 (0.6–10.0)	0.3–1.2
CT (pg/ml)	1.3 (0.5–3.3)	0.0–9.5

Continuous variables were presented as mean ± standard deviation. Non-normal distribution data were presented as median (range).
ALP, alkaline phosphatase; AST, aspartate aminotransferase; ATG, antithyroglobulin antibodies; ATPO, antithyroid peroxidase autoantibody; CT, calcitonin; FT3, free triiodothyronine; FT4, free thyroxine; GGT, glutamyl transpeptidase; Hb, hemoglobin; INR, international normalized ratio; NA, not applicable; rT3, reverse triiodothyronine; TSH, thyroid stimulating hormone; TT3, total-triiodothyronine; TT4, total thyroxine; TG, thyroglobulin; WBC, white blood cell count.

Changes Clinical Characteristics Before and After PE Treatment

In our study, the number of PE procedures for each patient was a median of 5 procedures ranging from 1 procedure to 13 procedures; the frequency of the PE procedures for each patient was a median of 2 procedures/week, ranging from 1 procedure/week to 3 procedures/week. The duration from first PE to last PE treatment was a median of 2 weeks, ranging from 1 to 10 weeks. The total number of PE procedures were 40 procedures in this study, but only 16 procedures had characteristics data before and after PE treatment. Table 2 shows the characteristics of pre-PE and post-PE treatment. The levels of hemoglobin, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase, total bilirubin, direct bilirubin, alkaline phosphatase, glutamyl transpeptidase, MELD scores, free triiodothyronine (FT3), free thyroxine (FT4), antithyroid peroxidase autoantibody and serum TRAbs after PE treatment were significantly lower than before PE treatment ($P < .05$, Figure 2).

Changes Clinical Characteristics Before and After Iodine-131 Treatment

In our study, the number of iodine-131 treatment for each patient was a median of 1 procedure ranging from 1 procedure to 4 procedures. Table 3 shows the characteristics of pre-131I and post-131I treatment. The level of total

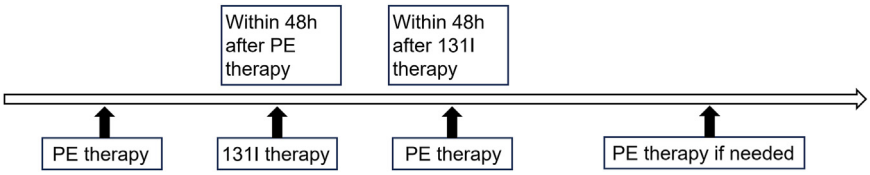

Figure 1. The treatment process diagram of the patients.

bilirubin at 3 months post-131I treatment was significantly lower than pre-131I treatment ($P = .0200$, Figure 3A). However, there was no significantly significant difference between the level of total bilirubin at pre-131I treatment and at 1-month post-131I treatment ($P > .05$). The level of direct bilirubin at 3 months post-131I treatment was significantly lower than pre-131I treatment ($P = .0200$, Figure 3B). However, there was no significantly significant difference between the level of direct bilirubin at pre-131I treatment and at 1-month post-131I treatment ($P > .05$). There was no significantly significant difference between the level of FT3 at pre-131I treatment and at 3-month post-131I treatment, and the same was the level of FT4.

Discussion

Graves' hyperthyroidism is a pathological disorder in which excess thyroid hormone is synthesized and secreted by the thyroid gland. The prevalence of liver biochemical abnormalities in patients with untreated hyperthyroidism widely ranging from 15% to 76%.[11] The suggested causes of liver dysfunction include direct hepatocyte injury, comorbid heart failure, pre-existing liver disease, drugs including antithyroid medications and associated autoimmune conditions, especially in the setting of GD. Although, some patients may have a pattern of mild liver injury, about 1%–2% can have fulminant hepatitis.[11] If the GD patient has severe liver injury, it should prompt serious reconsideration of ATD or total thyroidectomy therapy. Although there are not much data, RAI therapy may be the best option for them.[12] There is still no evidence to support the safety of RAI treatment among patients on the liver-transplant waiting list. Once a patient with cirrhosis has experienced an index complication such as ascites, hepatic encephalopathy, or variceal hemorrhage or hepatocellular dysfunction results in a MELD Score $\geq$15, evaluation for liver transplantation

Table 2. Laboratory Test Results of Graves' Hyperthyroidism Patients With Severe Liver Injury Before and After Plasma Exchange Treatment

Characteristics	Pre-PE	Post-PE	Reference ranges	*P* Value
WBC ($\times 10^9$/L)	7.6 ± 3.1	6.4 ± 1.7	3.5–9.5	.1726
Hb (g/L)	109.0 (82.0–122.0)	103.5 (79.0–113.0)	115.0–150.0	.0023[a]
Platelet count ($\times 10^9$/L)	151.4 ± 84.6	133.1 ± 80.6	125.0–350.0	.0085[a]
ALT (U/L)	69.5 (20.0–299.0)	53.0 (20.0–156.0)	7.0–40.0	.0002[a]
AST (U/L)	54.0 (21.0–388.0)	44.0 (20.0–298.0)	13.0–35.0	.0032[a]
Total bilirubin (μmol/L)	325.2 (177.4–698.0)	269.4 (120.9–516.7)	≤21.0	.0002[a]
Direct bilirubin (μmol/L)	294.0 (167.5–651.9)	243.1 (112.3–432.5)	≤8.0	.0004[a]
ALP (U/L)	132.8 ± 40.5	107.3 ± 29.4	35.0–100.0	.0004[a]
GGT (U/L)	33.5 (15.0–106.0)	29.5 (14.0–62.0)	7.0–45.0	.0110[a]
Serum creatinine (μmol/L)	36.0 (26.0–84.0)	34.0 (24.0–89.0)	57.0–97.0	.3683
INR	1.2 (1.0–3.1)	1.2 (0.9–2.0)	0.9–1.2	.0764
MELD scores	21.1 ± 5.0	19.5 ± 3.8	NA	.0010[a]
TT3 (nmol/L)	4.9 (2.1–10.0)	3.8 (1.9–10.0)	1.3–3.1	.2061
TT4 (nmol/L)	203.7 ± 49.6	195.5 ± 54.8	66.0–181.0	.1294
FT3 (pmol/L)	22.9 ± 17.5	19.7 ± 14.7	3.1–6.8	.0137[a]
FT4 (pmol/L)	80.1 (34.7–100.0)	73.1 (30.2–100.0)	12.0–22.0	.0312[a]
TG (ng/mL)	107.0 (3.9–500.0)	56.5 (6.5–500.0)	3.5–77.0	.1562
ATPO (IU/mL)	91.6 (9.0–600.0)	67.8 (9.0–600.0)	<34.0	.0234[a]
ATG (IU/mL)	15.9 (14.0–3986.0)	17.3 (12.6–2586.0)	<115.0	.7002
TRAb (IU/L)	11.1 (3.6–40.0)	7.2 (2.4–33.2)	<1.8	.0010[a]

Continuous variables were presented as mean ± standard deviation. Non-normal distribution data were presented as median (range).
ALP, alkaline phosphatase; AST, aspartate aminotransferase; ATG; antithyroglobulin antibodies; ATPO, antithyroid peroxidase autoantibody; FT3, free triiodothyronine; FT4, free thyroxine; GGT, glutamyl transpeptidase; Hb, hemoglobin; INR, international normalized ratio; NA, not applicable; TG, thyroglobulin; TT3, total-triiodothyronine; TT4, total thyroxine; WBC, white blood cell count.
[a]Statistically significant difference.

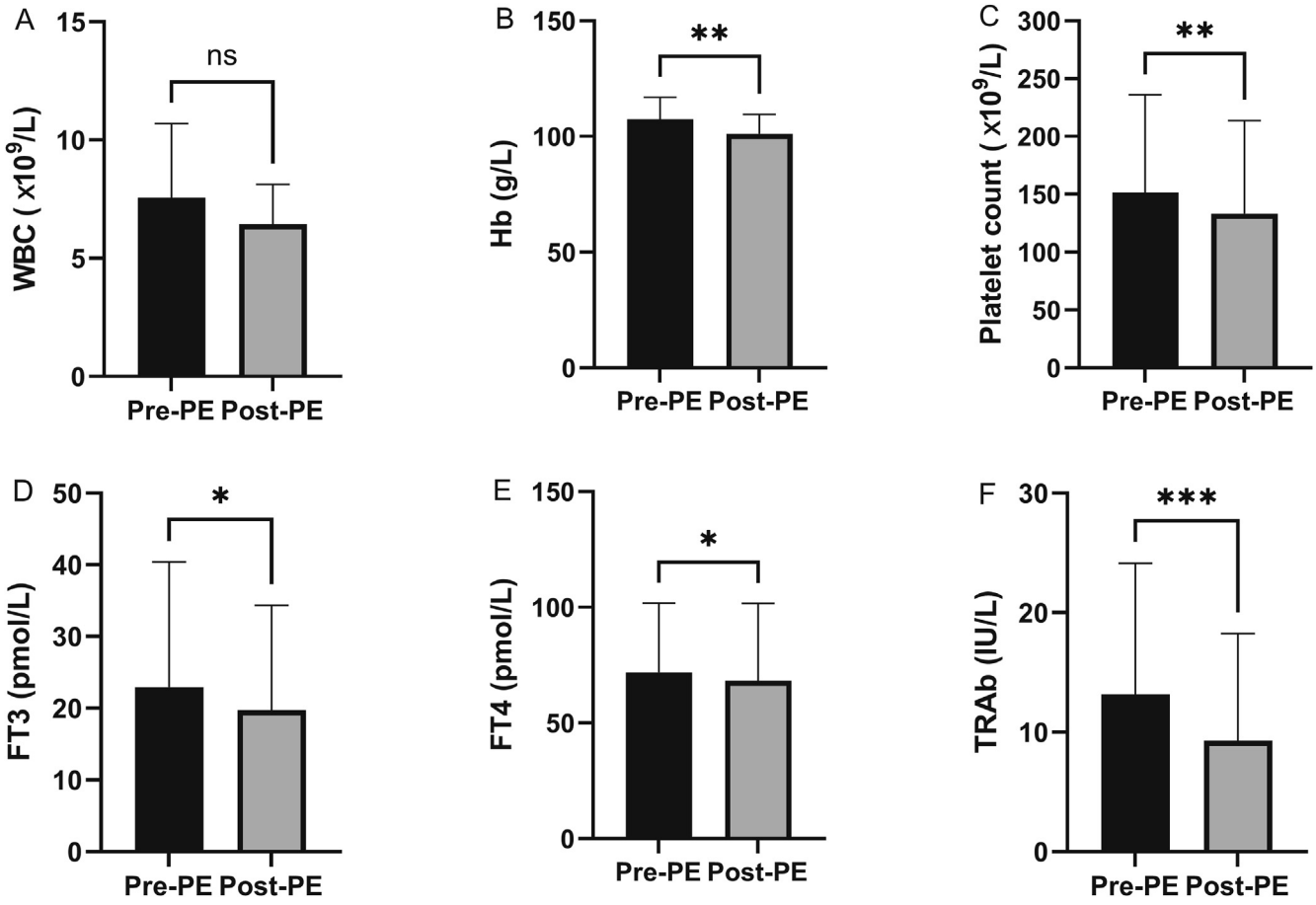

Figure 2. Changes clinical characteristics before and after PE treatment. Panel A: the level of white blood cell count before and after PE treatment. Panel B: the level of hemoglobin before and after PE treatment. Panel C: the level of platelet counts before and after PE treatment. Panel D: the level of FT3 before and after PE treatment. Panel E: the level of FT4 before and after PE treatment. Panel F: the level of TRAb before and after PE treatment.

should be considered.[13] In our study, the mean of MELD scores of the patients with hyperthyroidism at baseline was above 20. Moreover, after discontinuation of ATD treatment and general treatment, there was no improvement in liver function. However, after RAI combined with PE treatment, both liver function and thyroid function improved. These results suggest that RAI combined with PE treatment is safe in Graves' hyperthyroidism patients with severe liver injury whose average MELD scores were greater than 20.

We found that the levels of ALT, aspartate aminotransferase, total bilirubin, direct bilirubin, alkaline phosphatase, glutamyl transpeptidase, MELD scores, FT3, FT4, antithyroid peroxidase autoantibody, and TRAb after PE treatment were significantly lower than before PE treatment. These results suggest that both liver function and thyroid function improved after PE treatment. In terms of adverse reactions to PE treatment, PE treatment leads to a decrease in the levels of hemoglobin and thrombocytopenia, but does not reduce the levels of white blood cell count. A case report found that a GD patient received MMI, then developed drug-induced liver injury evidenced by an increase in liver enzymes (ALT up to 1023 U/L) and the elevation of total bilirubin to 258.21 μmol/L, so MMI was stopped and 5 procedures of therapeutic PE were performed, which improved the signs and symptoms of hyperthyroidism and retained the thyroxine hormone within the normal range.[14] Finally, thyroidectomy was performed successfully without serious complications, therapeutic PE is a safe and effective bridging therapy for GD patients who require thyroidectomy but cannot tolerate ATDs.[14] A case report shows that a patient with a thyroid storm due to untreated Graves' disease complicated by cholestatic hepatic injury (total bilirubin 233.2 μmol/L), received oral carbimazole, prednisolone, propranolol and Lugol's iodine, and was feeling generally well with resolution of the jaundice and clinically euthyroid on a follow-up assessment 10 weeks later.[15] Another case report shows that a patient with severe hyperthyroidism-associated hepatotoxicity, in which adjuvant therapies, including glucocorticoids, saturated solution of potassium iodide, and cholestyramine, were used as a bridge to definitive therapy with thyroidectomy.[16] Another case report shows that a GD patient with total bilirubin 322.4 μmol/L discontinued MMI, received 3 procedures of

Table 3. Laboratory Test Results of Graves' Hyperthyroidism Patients With Severe Liver Injury Before and After I131 Treatment

Characteristics	Before I131 treatment	After I131 treatment	One wk after I131 treatment	One mo after I131 treatment	Three mo after I131 treatment	Reference ranges	*P* Value
WBC ($\times 10^9$/L)	6.2 ± 3.3	6.2 ± 2.3	5.7 ± 2.2	4.9 ± 1.6	4.5 ± 1.2	3.5–9.5	.6989
Hb (g/L)	98.4 ± 19.7	96.2 ± 19.6	101.0 ± 17.4	98.0 ± 8.8	107.8 ± 27.8	115.0–150.0	.9051
Platelet count ($\times 10^9$/L)	112.0 (73.0–302.0)	133.0 (93.0–311.0)	138.0 (60.0–329.0)	132.0 (111.0–258.0)	81.5 (57.0–169.0)	125.0–350.0	.4901
ALT (U/L)	33.5 (19.0–158.0)	29.0 (20.0–186.0)	42.5 (17.0–152.0)	34.0 (27.0–38.0)	21.5 (12.0–42.0)	7.0–40.0	.6227
AST (U/L)	48.5 (24.0–332.0)	46.0 (41.0–348.0)	44.0 (36.0–210.0)	37.0 (28.0–59.0)	32.5 (23.0–48.0)	13.0–35.0	.1098
Total bilirubin (μmol/L)	261.5 (181.3–481.3)	213.2 (143.0–460.0)	211.2 (100.3–440.9)	73.00 (16.0–496.9)	27.00 (8.8–312.2)	≤21.0	.0374[a]
Direct bilirubin (μmol/L)	239.4 (115.0–420.2)	184.0 (85.0–413.0)	154.6 (71.9–382.4)	54.5 (11.4–427.8)	15.4 (4.4–285.3)	≤8.0	.0338[a]
ALP (U/L)	122.1 ± 44.1	141.3 ± 35.3	122.0 ± 39.7	199.3 ± 82.0	139.3 ± 40.1	35.0–100.0	.3258
GGT (U/L)	28.9 ± 8.6	30.8 ± 12.0	34.1 ± 12.7	44.5 ± 20.7	48.3 ± 40.7	7.0–45.0	.7553
Serum creatinine (μmol/L)	44.6 ± 16.9	43.8 ± 15.6	43.5 ± 14.4	42.7 ± 17.1	76.0 ± 41.2	57.0–97.0	.5490
INR	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.2	1.3 ± 0.3	1.6 ± 0.5	0.9–1.2	.5683
MELD scores	19.5 ± 2.5	19.3 ± 3.4	18.2 ± 3.1	17.5 ± 5.7	17.2 ± 8.0	NA	.8828
TSH (mIU/L)	0.0 (0.0–0.2)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–65.4)	0.3–4.2	.1631
TT3 (nmol/L)	3.9 ± 2.5	3.8 ± 1.4	3.8 ± 2.3	4.5 ± 4.1	3.1 ± 2.5	1.3–3.1	.8776
TT4 (nmol/L)	185.8 ± 73.7	192.8 ± 53.4	184.2 ± 61.8	178.0 ± 91.5	125.5 ± 67.1	66.0–181.0	.3991
FT3 (pmol/L)	12.3 (6.1–41.0)	12.3 (7.9–32.5)	6.8 (5.3–35.4)	4.9 (2.9–49.5)	6.8 (1.9–29.6)	3.1–6.8	.4572
FT4 (pmol/L)	54.0 ± 39.7	53.6 ± 35.1	49.4 ± 36.1	37.1 ± 36.6	36.9 ± 37.6	12.0–22.0	.7028
TG (ng/mL)	11.5 (1.1–500.0)	47.1 (10.9–500.0)	20.5 (12.2–500.0)	379.5 (259.0–500.0)	63.8 (0.0–166.0)	3.5–77.0	.3694
ATPO (IU/mL)	150.2 ± 128.1	115.1 ± 90.3	126.7 ± 107.8	139.3 ± 82.5	251.3 ± 274.6	<34.0	.9780
ATG (IU/mL)	43.1 (15.5–1434)	32.1 (14.0–1346)	23.9 (11.6–1302)	38.7 (2.4–2122)	20.2 (13.8–1625.0)	<115.0	.8782
TRAb (IU/L)	7.6 (2.8–23.7)	6.4 (3.7–24.2)	5.6 (2.8–23.5)	9.4 (2.5–16.3)	13.8 (3.3–40.0)	<1.8	.4491

Continuous variables were presented as mean ± standard deviation. Non-normal distribution data were presented as median (range).
ALP, alkaline phosphatase; AST, aspartate aminotransferase; ATG, antithyroglobulin antibodies; ATPO, antithyroid peroxidase autoantibody; FT3, free triiodothyronine; FT4, free thyroxine; GGT, glutamyl transpeptidase; Hb, hemoglobin; INR, international normalized ratio; NA, not applicable; TG, thyroglobulin; TT3, total-triiodothyronine; TT4, total thyroxine; WBC, white blood cell count.
[a]Statistically significant difference.

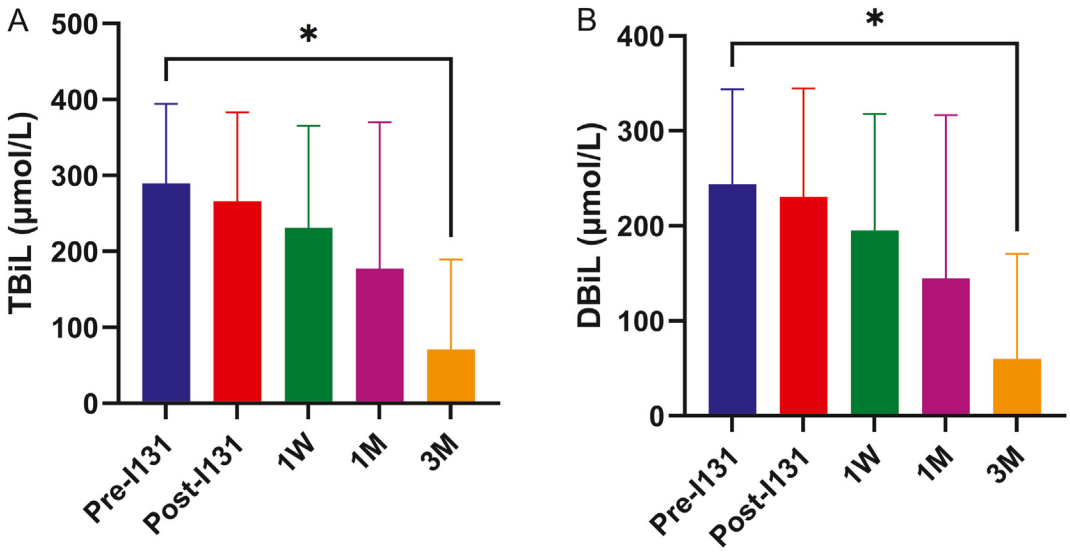

Figure 3. The level of bilirubin before and after iodine-131 treatment. Panel A: the level of total bilirubin before and after iodine-131 treatment. Panel B: the level of direct bilirubin before and after iodine-131 treatment. *Statistically significant difference.

therapeutic PE, and about 3-month glucocorticoid treatment, then her cholestatic jaundice was recovered.[17] Corticosteroids may be a salvage treatment option, but the use of glucocorticoids in patients with liver failure increases the risk of infections such as cytomegalovirus infection.[18,19]

In our study, the level of total bilirubin at 3 months post-131I treatment was significantly lower than pre-131I treatment. There was no significant deterioration of liver function after RAI therapy. A retrospective study included patients with untreated hyperthyroidism among whom biochemical findings noted hepatic dysfunction and excluded those with concomitant liver disease.[20] Liver dysfunction was moderate and severe in 8 of 17 and 2 of 17 cases, respectively. RAI was indicated in 15 of 17 cases, and follow-up liver function tests were performed in 11 cases. They all had normalized liver function once euthyroidism restored.[20] A previous study presented a case of a GD patient with severe pulmonary hypertension and cholestatic liver injury (total bilirubin of 13 mg/dL), which resolved with propranolol, MMI, furosemide, dexamethasone, and iodine treatment in about 3 months.[21] Another previous study demonstrated that the age, duration of Graves hyperthyroidism, FT3 level, and TRAb concentration were the risk factors predicting hepatic dysfunction.[22] The patients with mild hepatic dysfunction or hepatocellular injury type were more likely to attain normal liver function after RAI treatment.[22] After RAI treatment, liver function was more likely to return to normal in the cured group of patients compared with the uncured group.[22]

Our study has several limitations. First, there may be bias in a single-center retrospective study and some data are incomplete. Second, the sample size is small given the single-center experience and rarity of the case presentation, limiting the significance of the findings. Lastly, 3-month follow-up time is relatively short, we don't know when thyroid function will recover. This was also an interesting phenomenon, although thyroid function did not return to normal at 3 months, liver function improved, and the specific mechanism is still unclear, possibly due to the alleviation of immune-mediated liver damage. Further large-scale prospective studies are needed to confirm the findings.

Conclusion

Our study enrolled Graves' hyperthyroidism patients with severe liver injury whose average MELD scores were greater than 20, and shows that liver function test can recover on about 3 months treated iodine-131 combined with PE therapy.

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Conflicts of Interest:
The authors disclose no conflicts.

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Ethical Statement:
This retrospective study was performed in accordance with the Helsinki Declaration and was approved by the Ethical Committee of Huashan Hospital, Fudan University (2024-679). All the patients or their representatives provided written informed consent for the study.

Data Transparency Statement:
Identifying/confidential patient data however will not be shared. Data available on request due to privacy/ethical restrictions.

Reporting Guidelines:
Helsinki Declaration.