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Partial radiofrequency ablation of the spleen in thalassemia

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PURPOSE
To investigate the efficiency of partial radiofrequency ablation of the spleen in patients with thalassemia major and intermedia.

MATERIALS AND METHODS
Partial radiofrequency ablation of the spleen was performed in 19 thalassemic patients (10 females, nine males) with a mean age of 12.7 years (age range, 7–30 years). This group of patients consisted of 11 patients with thalassemia major and nine with thalassemia intermedia. The procedure was performed under intravenous sedation and was complete in 29–35 min.

RESULTS
The ratio of the ablated volume to the whole spleen ranged from 5.3% to 23% (mean, 9.83±5.56%). A significant increase was found in the platelet count after radiofrequency ablation of the spleen ($P = 0.002$). No statistically significant difference was found in hemoglobin levels ($P = 0.171$) or transfusion intervals ($P = 0.054$) before and after radiofrequency ablation. Additionally, no statistically significant relationship was observed between the ablation ratio and hemoglobin levels ($P = 0.233$) and between the ablation ratio and transfusion interval ($P = 0.822$). No major complication occurred due to this interventional procedure.

CONCLUSION
A single percutaneous radiofrequency ablation of the spleen reduces thrombocytopenia in thalassemic patients with splenomegaly but does not change the hemoglobin levels or transfusion intervals.

Key words: • *ablation techniques* • *thalassemia* • *splenomegaly*

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Thalassemia is an inherent hemoglobinopathy that presents as intermediate to severe anemia, bone transformation, and splenomegaly (1, 2). Massive splenomegaly and hypersplenism causing leukopenia, thrombocytopenia, and an increasing transfusion requirement are often observed in young patients whose transfusion regimens are sporadic (3). Splenic enlargement is accompanied by symptoms such as left upper quadrant pain or early satiety. Massive splenomegaly may also lead to splenic rupture. Splenectomy may be indicated in some patients to decrease transfusion requirements. However, it may be delayed or prevented by optimal clinical management of the transfusion protocol (3).

So far, total splenectomy has been the most commonly applied surgical procedure (3), but partial splenectomy has been used in some centers to preserve part of the spleen's immune function while reducing the degree of hypersplenism (4). Splenectomy has its own complications. Perioperative complications include bleeding, atelectasis, and subphrenic abscess (3). The major long-term risk after splenectomy is overwhelming sepsis that may increase up to 30-fold compared with the normal population (3, 4). Other probable complications are thrombophilia and pulmonary hypertension (3).

Radiofrequency ablation (RFA) has been performed to reduce the size of tumors of various organs as a minimally invasive treatment method (5–8). Thermal coagulative necrosis induced by radiofrequency (RF) can reduce the parenchyma of organs; thus, RFA can also be an effective therapeutic technique for hypersplenism. Thus far, few reports have existed regarding spleen RFA experiments in animal or human cases (9–13). Only one study has been conducted on thalassemic patients with the aim of exploring the feasibility, safety, and efficacy of spleen RFA in patients with thalassemia intermedia (10).

We conducted this study to investigate the applicability and efficacy of RFA in partial splenectomy of patients with thalassemia major and intermedia.

Materials and methods

Patient population

This study was approved by the institutional research ethics committee. Informed consent was received from all patients if they were considered adults. For younger patients, the corresponding doctor informed their parents about every aspect of this interventional procedure, and informed consent was received from parents. RFA of the spleen was performed in 19 thalassemic patients with either thalassemia major (eight patients) or thalassemia intermedia (11 patients) between March 2008 and December 2008. The diagnosis of thalassemia was based on hemoglobin electrophoresis of blood samples and

the age at which the patient began to receive transfusions. The enlarged spleen was confirmed in clinical examinations and ultrasonographic studies. In our patients, the indication for partial splenectomy was hypersplenism manifested by splenomegaly, leukopenia, thrombocytopenia, and anemia requiring frequent transfusions.

Procedure

All patients fasted for 12 hours before the start of the procedure. A bolus dose of prophylactic ceftriaxone (Jaber Ebne Hayyan Pharmaceutical Company, Tehran, Iran) 50 mg/kg in children and 1 g in adults (intravenous [IV] infusion) was administered 10 min before the start of the procedure. Preoperative determination of the spleen dimension and the RF electrode insertion pathway was conducted by ultrasonography on the day of the interventional procedure. The procedures were performed under IV sedation and ultrasound guidance using a Zone ultrasound scanner (ZONARE Medical Systems, Mountain View, California, USA). Three internally cooled needles (Celon ProSurge plus, Celon AG Medical Instruments, Teltow, Germany) of a bipolar RF system (Olympus Celon Power System, Celon AG Medical Instruments) were placed simultaneously into the deep splenic parenchyma far from its hilum or surface to avoid vascular injury or subcapsular hematoma. The needle's shaft diameter was 3.3 mm, with a 15 G shaft length (150 mm), and the active tips of the needles were 3–4 cm in length. Needles were placed with a 3-cm distance from one another in a triangle formation. Each needle was active in two poles, and the splenic tissue between needles was ablated. The highest power of the RF system was set at 250 W in the impedance-control mode. Chilled saline was circulated during the RFA procedure to prevent tissue boiling and cavitation immediately adjacent to the needle. The temperature of the chilled saline was approximately 20°C. Each needle ablates the tissue around its active tip in a cylindrical shape 1–1.5 cm in diameter. Once a location was assumed to be coagulated (after delivery of about 60 kJ of thermal energy), the RF system was held and the needle was withdrawn and placed in another position. In most cases, this withdrawal was partial, i.e., the needle was inserted again with a different angulation without exiting the splenic capsule, but in some rare cases we had to completely withdraw the needle and reinsert it again. Immediately before complete withdrawal of the needles, the saline infusion of the cool-tip system was stopped; thus, the needle tract became coagulated, reducing the possibility of bleeding or subcapsular hematoma. The procedure time was 29–35 min (mean time, 30.21±1.18 min).

The adult patients were given 100 mg celecoxib (Darou Pakhsh Pharma Chem. Company, Tehran, Iran) twice daily to control pain. The dose of celecoxib for children weighing between 10 and 25 kg was 50 mg twice daily, and children weighing 25 kg or more received the adult dose. Cefixime (Jaber Ebne Hayyan Pharmaceutical Company) at doses of 10 mg/kg daily for children and 400 mg daily for adults was administered for a seven-day period after discharge.

Patient follow-up

All patients were closely followed for approximately six months. Contrast-enhanced computed tomography (CT) using iohexol (240 mg I/mL, GE Healthcare, Princeton, New Jersey, USA) was performed for each patient one month after RFA. The whole-spleen volume and volumes of the ablated zones were measured after RFA, and the ratio of the ablated areas relative to the whole spleen was calculated. CT was performed using a multislice CT scanner (Somatom Sensation 64-slice, Siemens AG, Forchheim, Germany). The images were reviewed on a workstation (Syngo, Siemens AG), where the contours of the spleen and the ablated areas were outlined on 5-mm images obtained through the entire spleen. Patients' spleen total volume and its ablated volume were calculated using spiral CT scan images.

Statistical analysis

To evaluate the change in parameters before and after RFA, we used the Wilcoxon signed-rank test. We used the Spearman's rank correlation coefficient to study the correlation between the ablated ratio and the transfusion intervals as well as hemoglobin levels after RFA. All statistical analyses were performed using a software (Statistical Package for Social Sciences, version 17.0, SPSS Inc., Chicago, Illinois, USA). *P* values less than 0.05 were considered to be statistically significant.

Results

Ten patients (52.6%) were female, and nine (47.4%) were male. Eight patients (42.1%) and 11 patients (57.9%) were beta thalassemia intermedia (TI) and beta thalassemia major (TM), respectively. The mean hemoglobin level for the patients before RFA was 8.5 g/dL (range, 6.5–11.8 g/dL). The baseline demographic data are presented in Table 1. On the postoperative CT, the ablated regions comprised hypodense areas scattered throughout the spleen, which had a central zone of hyperdensity (Fig.). No intrasplenic or perisplenic collection was observed.

The ratio of the volume of the ablated regions to that of the whole spleen ranged from 5.3% to 23.7% (mean, 9.83±5.56%; Table 2). Two patients (10.5%) showed a considerable increase (1.9 and 2.6 g/dL, respectively) in mean hemoglobin compared with before RFA. Additionally, in two other patients (10.5%), the time between transfusions was twice as long after RFA. A statistically significant difference was found between the platelet count before and after the spleen RFA ($P = 0.002$; Table 3). However, no statistically significant difference was found in the hemoglobin level ($P = 0.171$), transfusion intervals ($P = 0.054$), or white blood cell count ($P = 0.26$) between before and after RFA (Table 3).

We calculated the Spearman's rank correlation between the ablation ratio, transfusion intervals, and hemoglobin level after RFA. No statistically significant relation was observed between the ablation ratio and hemoglobin level ($P = 0.233$) and between the ablation ratio and transfusion interval ($P = 0.822$). The data are summarized in Table 4.

No postoperative mortality or major complication occurred due to this interventional procedure. Minor bleeding around the electrodes, which ceased spontaneously, occurred in two patients. One subject complained of acute abdominal pain for a period

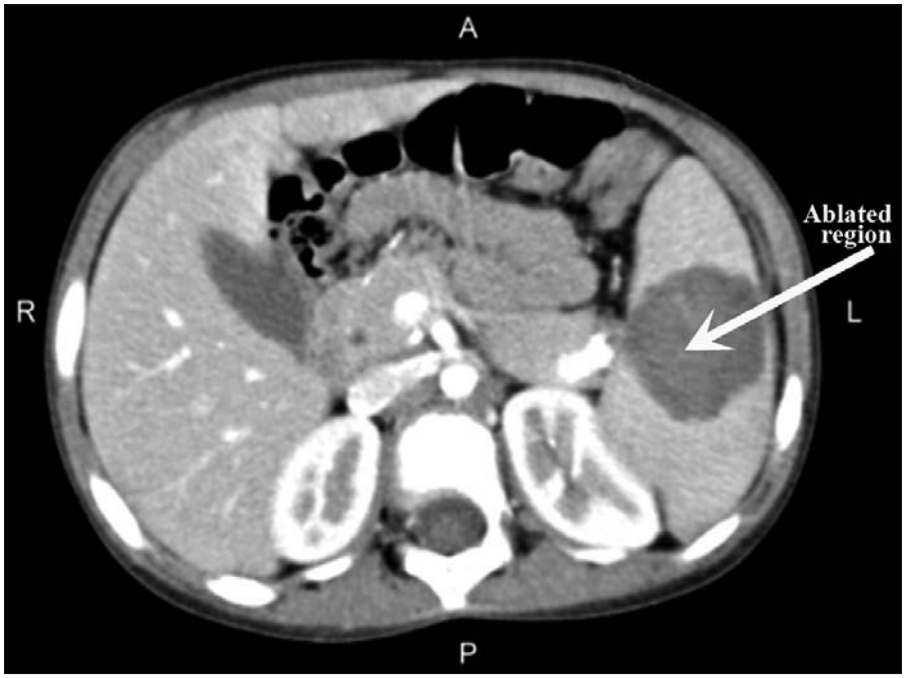

Figure. A postoperative contrast enhanced CT image of an eight-year-old patient who underwent RFA.

of 36 hours after RFA, but abdominal ultrasound revealed no thrombosis or collection. The mean hospital stay after ablation was six hours. Up to September 2011, six patients underwent total splenectomy (one child and five adults), and two patients had splenic embolization (both adults).

Discussion

Thalassemic patients usually require a regular blood transfusion regimen in addition to treatment with iron chelators. Most of these patients ultimately develop some degree of hypersplenism that increases their need for blood transfusion (4). Although surgical splenectomy significantly reduces the transfusion requirements in patients with thalassemia, it makes the patients, specifically during childhood, susceptible to overwhelming post-splenectomy infections and portal thrombosis (9, 14). Another disadvantage of total splenectomy is that the complete loss of the spleen induces thrombophilia and increases the risk of thromboembolic complications (4).

RFA has been performed to treat many kinds of malignant and benign tumors (5–8, 15–19); however, only a few reports have investigated the use of spleen RFA for partial splenectomy (9–12). These studies have established the safety and effectiveness of RF in reducing splenic tissue and in the management of hypersplenism. Additionally, they have indicated that such a method could be temporarily effective by postponing the total surgical splenectomy, giving time to children to grow up and get past the period in which they are vulnerable to overwhelming infections caused by total splenectomy (9, 10, 12). We performed a partial splenectomy using minimally invasive RFA under the guidance of ultrasonography in a small group of thalassemic patients with acceptable outcome.

Although the ablated volume in our study was comparatively small (mean, 9.83% of the whole spleen), a significant increase was noted in the mean platelet count after RFA among our patients, which is in line with other studies (9, 11, 12). By comparing the results of our study with those of Rasekhi et al., (12) it can be noted that despite a statistically significant increase in the mean platelet count in both studies, the amount of increase is somehow related to the ablated ratio. With a mean ablation ratio of 9.83%, the mean platelet count among our patients increased from 174 000/μL to 239 000/μL; however, in their study, with a mean ablation ratio of 32.3%, the mean platelet count increased from 201 000/μL to 320 000/μL (12).

We noticed increased hemoglobin levels and longer transfusions intervals in two younger patients with a high ablated volume compared with the whole spleen ratio, but we found no statistically significant difference in the hemoglobin levels and transfusion intervals between before and after RFA among our patients. We

Table 1. The baseline characteristics of patients entering the study

Parameter	Result
Age (years)	17.7±7.9 (4–30)
Gender (female/male)	10/9 (52.6)
Type of thalassemia	
TI	8 (42.1)
TM	11 (57.9)
White blood cells (/μL)	7034±3060 (3100–12 100)
Hemoglobin (g/dL)	8.5±1.3 (6.5–11.8)
Platelet (/μL)	173 732±79 782 (50 900–311 000)
Transfusion period (days)	17.2±4.7 (10–30)

TI, thalassemia intermediate; TM, thalassemia major.
Data are given as mean±SD (range) or n (%).

Table 2. Descriptive statistics of ablated and total splenic volume

	Minimum	Maximum	Mean	SD
Spleen volume (mL)	598.0	6900.0	3497.7	1466.9
Ablated volume of spleen (mL)	141.90	439.0	288.19	93.18
Ablated to total ratio (%)	5.3	23.7	9.83	5.46

SD, standard deviation.

Table 3. The changes in hemoglobin, WBC count, platelet count, and transfusion interval after RFA

				WBC (/μL)		Hemoglobin (g/dL)		Platelet (/μL)		Transfusion period (days)	
Case	Age	Gender	Type of thalassemia	Before	After	Before	After	Before	After	Before	After
1	10	Female	Alpha	7600	7700	8.3	8.7	310 000	320 000	14	30
2	15	Male	TI	9800	10 200	10.2	10.5	78 000	178 000	20	15
3	26	Female	TI	12 100	9400	8.0	6.6	50 900	112 000	14	20
4	4	Female	TI	11 700	11 200	11.8	11.9	255 000	287 000	20	14
5	20	Female	TI	3800	9000	8.6	9.2	169 000	162 000	21	20
6	24	Male	TI	9300	8400	7.7	8.0	178 000	171 000	15	15
7	27	Male	TI	4700	4000	8.0	7.9	214 000	173 000	15	15
8	8	Female	TI	6300	9300	8.0	8.6	311 000	429 000	20	40
9	7	Female	TM	10 500	9700	7.1	8.0	110 000	187 000	15	18
10	21	Male	TM	9200	9000	8.1	10.7	135 000	222 000	20	20
11	20	Female	TM	5200	8000	8.2	8.5	65 000	210 000	15	15
12	22	Male	TM	3100	6200	7.1	9.7	103 000	96 000	20	20
13	27	Male	TM	4000	4600	10.3	9.4	135 000	145 000	14	16
14	14	Male	TM	4100	4500	9.8	7.0	189 000	220 000	20	25
15	18	Female	TM	4100	9300	8.3	8.2	253 000	392 000	20	20
16	23	Male	TM	6300	6174	6.5	8.1	134 000	141 000	10	21
17	11	Male	TM	7302	6155	8.1	6.5	158 000	239 000	10	14
18	9	Female	TM	11 066	11 545	8.4	11.7	285 000	440 000	14	20
19	30	Female	TM	3469	7921	8.6	8.8	168 000	420 000	30	30
Mean	17.7			7034	8016	8.5	8.8	173 732	239 158	17.2	20.4
SD	7.9			3060	2210	1.3	1.5	79 782	110 398	4.7	6.7
Median	20			6300	8400	8.2	8.6	168 000	210 000	15	20
P value[a]				0.26		0.171		0.002		0.054	

WBC, white blood cell; RFA, radiofrequency ablation; TM, thalassemia major; TI, thalassemia intermediate; SD, standard deviation.
[a]*P* for the change based on Wilcoxon signed rank test

Table 4. Spearman's rank correlation coefficient (r) of different factors with ablated ratio of spleen (%)

	r	*P*
Transfusion interval after RFA	0.287	0.233
WBC after RFA	0.142	0.561
Hemoglobin after RFA	-0.055	0.822
Platelet after RFA	0.186	0.445

RFA, radiofrequency ablation; WBC, white blood cell.

also did not have any transfusion-free patients after RFA. Rasekhi et al. (12) have reported that 20% of their patients became transfusion free after partial RFA of spleen. We think the difference in outcomes is the result of the smaller ablation ratio in our study (9.83%) compared with that in their study (32.3%) (12). This suggests the increase in hemoglobin levels is related to the ratio of the ablated spleen. Although we found no significant correlation between the ablation ratio and hemoglobin level after RFA using Spearman's rank correlation coefficient, this lack of correlation might be due to the narrow range of the ablation ratio (5.3% to 23.7%) or the limited number of cases in our study.

No mortality or major complication such as fever, splenic abscess, or splenic rupture was observed among our patients. We only encountered one instance of acute abdominal pain for a period of 36 hours after RFA. However, in follow-up monitoring using CT and ultrasonography for this patient, we found no source for the pain, including portal thrombosis or collection. Analgesics and antibiotics were prescribed in this case, and the pain subsided after 36 hours.

Some studies have indicated that the histology of the splenic remnant changes throughout the splenic parenchyma after RFA (20). The histopathological changes of splenic lesions caused by RFA include local coagulative necrosis, peripheral thrombotic infarction, and occlusion of vessels in the remaining normal splenic tissue, as well as deposition of extensive fibrous protein and disappearance of congestive splenic sinusoid, all of which seem to explain the spleen shrinkage (10, 13). However, we found no significant change in the size of the spleen after RFA. This may be due to the fact that the ablation ratio in our study was limited to less than 10% of the total splenic volume, in contrast to studies with higher ablation ratios (8–10).

Our study has some limitations. After RFA of the spleen, abdominal CT was performed only once as a follow up for patients' safety. Additionally, because we performed RFA using three cool-tip needles of a bipolar RF system, which is a relatively new technique that has not been used before for partial splenectomy, we were cautious about the volume of the ablated spleen so as to avoid probable intraoperative complications. Thus, in the present study, we did not achieve an optimal ratio of the ablated volume to the whole spleen volume in just one session. This may explain the absence of any correlation between the ablation ratio of the spleen and transfusion interval or hemoglobin levels after RFA.

In conclusion, percutaneous minimally invasive RFA of the spleen seems to be a safe and cost-effective therapeutic technique in thalassemic patients with hypersplenism. More extensive studies are still required to investigate the efficacy and safety of partial splenectomy using RFA in this group of patients.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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