Retrospective Study

Comparison of Efficacy and Safety of Lumbar Sympathetic Radiofrequency Thermocoagulation Versus Chemical Lumbar Sympathectomy in the Treatment of Cold Hypersensitivity in the Hands and Feet: A Retrospective Study

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Background: Cold hypersensitivity in the hands and feet (CHHF) is a disease characterized by abnormal cold in the limbs with limited treatment options. Compared to traditional drug therapy, lumbar sympathectomy is a new minimally invasive surgical method for treating CHHF.

Objectives: The present study aimed to compare the efficacy and safety of lumbar sympathetic radiofrequency thermocoagulation (RFT) and chemical lumbar sympathectomy (CLS) in treating CHHF.

Study Design: A single-center, retrospective, observational study.

Setting: Department of Anesthesiology and Pain Medicine, Jiaxing, China.

Methods: A total of 102 patients with CHHF who underwent lumbar sympathectomy from January 2016 to April 2020 were included in this study. According to the mode of operation, the patients were divided into 2 groups: CLS (n = 56) and RFT (n = 46). All patients were treated under the guidance of computed tomography (CT). The foot temperature (T) and peripheral perfusion index (PI) were compared between the 2 groups before and after treatment. The 2 groups' visual analog scale (VAS) scores were evaluated before the operation and 1 day, 1 month, 3 months, 6 months, and 1 year after the treatment. The postoperative recurrence rate of the 2 groups was observed 1 year after treatment. The short and long-term complications during the postoperative follow-up were recorded.

Results: All patients completed the operation successfully. No significant difference was noted in the gender, age, course of the disease, preoperative T and PI, and postoperative T and PI between the 2 groups ($P > 0.05$). The postoperative T and PI were significantly increased compared to preoperative in both groups ($P < 0.05$). No significant difference was observed in T and PI between the 2 groups ($P > 0.05$), and no significant difference was recorded in VAS scores between the 2 groups 1 day and 1 month after the treatment ($P > 0.05$). The VAS scores at 3 months, 6 months, and 1 year after the treatment were significantly lower in the RFT group compared to the CLS group ($P < 0.05$). During the 1-year follow-up, patients who received CLS had a higher risk of recurrence than RFT treatment ($P < 0.05$). The RFT group treatment of CHHF showed better long-term outcomes than the CLS group. About 12.5% of patients in the CLS group and 6.5% in the RFT group had postoperative complications, including pain at the puncture site and genitofemoral neuralgia. However, no severe complications or deaths were observed in either of the 2 groups.

Limitations: The was a single-center, retrospective, non-randomized study, which is a major limitation of this study.

Conclusions: Lumbar sympathetic RFT had better long-term efficacy, lower recurrence, and fewer complications than the chemical lumbar sympathectomy when treating CHHF.

Key words: Cold hypersensitivity, sympathetic, radiofrequency thermocoagulation, chemical lumbar sympathectomy

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Cold hypersensitivity in the hands and feet (CHHF) is a disease characterized by abnormal cold in the limbs, which mainly affects Asian women (1). Regardless of the external environment, the symptoms of CHHF are persistent, especially sensitivity to cold air conditioning. It reduces the quality of life and has a detrimental effect on the mental health of the patients. However, the etiology and pathogenesis are yet to be clarified. Previous studies have shown that the pathogenesis may be related to the decrease in limb blood perfusion caused by excessive vasoconstriction of blood vessels in the extremities (2). Therefore, the key to improving the symptoms of CHHF is to increase the blood supply of limbs.

The traditional treatments of CHHF are acupuncture and medicine with a specific curative effect (3-5). However, none of these therapeutic approaches have provided sustained or long-term relief to the disease. In a previous study, we used chemical lumbar sympathetic nerve block to treat CHHF. The data indicated that it is an effective treatment of CHHF and could significantly improve the symptoms of lower limb cold (6). However, the follow-up found that > 30 % of patients relapsed after the operation, which was challenging for the treatment. Hence, it is necessary to explore a new treatment to reduce the postoperative recurrence rate.

Reportedly, percutaneous radiofrequency lumbar sympathectomy is an effective method for treating diabetic peripheral neuropathy and lower limb complex regional pain syndrome type 1 (7,8). Next, we applied radiofrequency technology to the treatment of CHHF to destroy the lumbar sympathetic nerve for complete nerve damage accurately. The present study aimed to compare the efficacy and recurrence rate of lumbar sympathetic radiofrequency thermocoagulation (RFT) and chemical lumbar sympathectomy (CLS) in treating CHHF.

Methods

Patients

This retrospective study included 102 patients with CHHF who underwent lumbar sympathectomy at the Affiliated Hospital of Jiaxing University, Jiaxing, China, from January 2016 to April 2020. According to the mode of operation, the patients were divided into 2 groups: CLS (n = 56) and RFT (n = 46). This study was approved by the Ethics Committee of the Affiliated Hospital of Jiaxing University. All patients were informed about the risk and complications before treatment, and informed consent was obtained before participation in the study.

The inclusion criteria were as follows: age > 18 years; the lesions involved the lower extremities; no significant improvement was noted after conservative measures, drugs, and acupuncture treatment; preoperative visual analog scale (VAS) score was ≥ 4. The exclusion criteria were as follows: patients who did not accept surgery or withdraw from the study; patients with other diseases that may cause cold in the limbs (such as Raynaud's syndrome, hypothyroidism, vasculitis obliterans); pregnancy; patients with severe mental disorders and intellectual disability; blood coagulation disorders; severe organ diseases; local skin infection at the puncture site; allergy to local anesthetics and anhydrous ethanol.

Surgical Procedure

CLS and RFT were conducted under the guidance of computed tomography (CT). The patient was positioned on the CT treatment table with a thin pillow under the abdomen to expose the puncture point. The heart rate, noninvasive blood pressure, and blood oxygen saturation were monitored continuously, and the peripheral temperature (T) and perfusion index (PI, monitored by Masimo Radical-7 monitor) were recorded dynamically. A positioning grid was placed next to the spinous process of the lumbar spine. The third lumbar vertebra (L3) was identified by CT scan, and the punctured plane was the section with the bilateral transverse process. The puncture target was the anterolateral edge of the L3 vertebral body and the anterior medial edge of the psoas major muscle. The puncture path was designed using the CT tool ruler to target the puncture (Fig. 1A). Then, the puncture point was marked on the body surface. The local infiltration anesthesia was administered at the puncture site with 1% lidocaine hydrochloride.

In the CLS group, a 10-cm 22-gauge (G) puncture needle was slowly inserted into the target according to the set puncture path (Fig. 1B). A diagnostic block was performed by injecting a 3 mL local anesthetic containing the contrast agent after negative aspiration of blood, urine, or gas was obtained. CT scanning revealed that the local anesthetics were distributed in the anterior lateral side of the vertebral body and the anterior medial side of the psoas major muscle but did not enter the blood vessels and abdominal cavity (Fig. 1C). Moreover, the lower limbs changed from cold to warm, and the plantar T and PI increased. An equivalent of 5 mL anhydrous ethanol containing contrast agent was injected into both sides, respectively. After

the operation, the patients were observed in the supine position for 30 min. If there was no discomfort, the patient could return to the ward.

A 22-G, 15-cm radiofrequency puncture needle with a 1-cm active tip was utilized in the RFT group. According to the set puncture path (Fig. 2A), the needle was slowly inserted into the target. The puncture was complete when the puncture needle tip reached the anterior lateral side of the L3 vertebral body and the anterior medial side of the psoas major muscle (Fig. 2B). Subsequently, the puncture needle was fixed, and the needle core was pulled out. Negative aspiration of liquid or gas was effectuated, and the radiofrequency electrode was inserted along the sleeve. The sensation

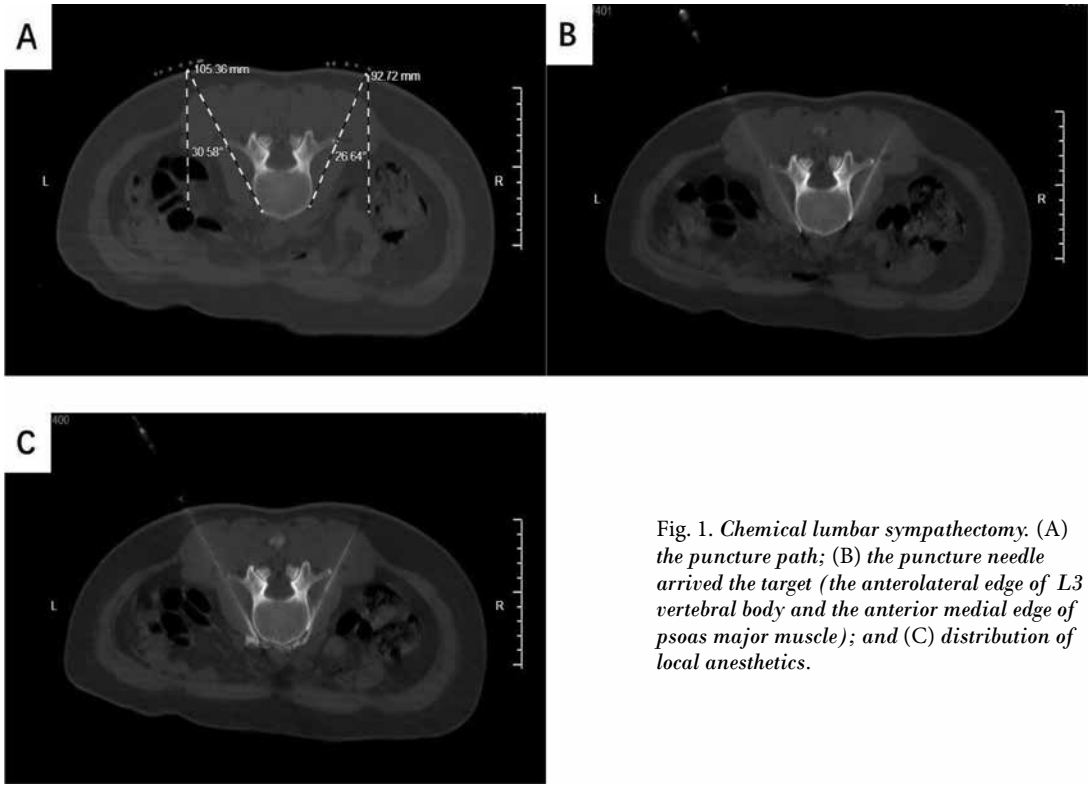

Fig. 1. *Chemical lumbar sympathectomy.* (A) *the puncture path;* (B) *the puncture needle arrived the target (the anterolateral edge of L3 vertebral body and the anterior medial edge of psoas major muscle); and* (C) *distribution of local anesthetics.*

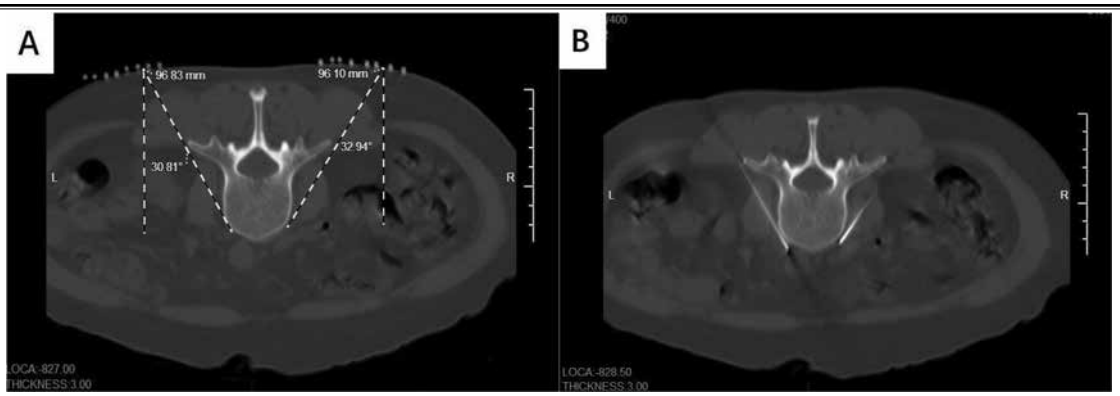

Fig. 2. *Lumbar sympathetic radiofrequency thermocoagulation.* (A) *the puncture path and* (B) *the radiofrequency puncture needle reached the target (the anterior lateral side of the L3 vertebral body and the anterior medial side of the psoas major muscle).*

test of 50 Hz and 0.5 mA and the movement test of 2 Hz and maximum 1.0 mA were carried out using the radiofrequency machine (Baylis Medical Company Inc., Toronto, ON, Canada) and without muscle convulsions in the spinal innervation area that could be treated by radiofrequency. For patients with unbearable pain, an appropriate amount of fentanyl (0.002 mg/kg) was given before radiofrequency to relieve the pain. Continuous RFT (95°C, 300 seconds) was conducted, following which the T and PI were increased, and when the patients felt that the limbs were warm, the operation was deemed completed. After the completion of RFT, the patient was laid in the supine position and observed for 30 min. Patients without obvious discomfort could return to the ward.

Observations and Follow-up

The primary outcomes included the VAS score and the recurrence rate postoperatively. The VAS score was used to assess the severity of CHHF, ranging from 0 (no coldness) to 10 (most coldness) (4,9). The follow-up was performed by outpatient or telephone on day 1 and 1 month, 3 months, 6 months, and 1 year after the treatment. The VAS score was measured at each visit or follow-up. The relapse was defined as a return to VAS ≥ 4 during follow-up. The recurrence rate is the number of relapses/total number of follow-up patients. The secondary outcomes included complications and adverse reactions. In addition, the patient's gender, age, course of the disease, T, and PI were recorded.

Statistical Analysis

SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) software was used for data analysis. The measurement data of normal distribution were described as mean ± standard deviation ($\bar{x} \pm sd$) and compared by t-test. Otherwise, median (interquartile range) is used for statistical description, and a non-parametric test was used for intergroup comparison. The qualitative data were presented as frequencies and percentages (%) and compared using the chi-square (χ^2) test. Recurrence-free survival was estimated using Kaplan-Meir survival analysis. The log-rank test was applied to compare the risk of developing recurrence between the 2 groups. *P*-values < 0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 109 patients were included in this study, following which 7 were lost to follow-up and 102 patients were included in the final analysis, i.e., 56 patients in the CLS group and 46 patients in the RFT group. The cohort consists of 70 women and 32 men. The flowchart of patient enrollment is shown in Fig. 3. No significant difference was observed in the gender, age, course of the disease, preoperative T and PI, and postoperative T and PI between the 2 groups ($P > 0.05$, Table 1).

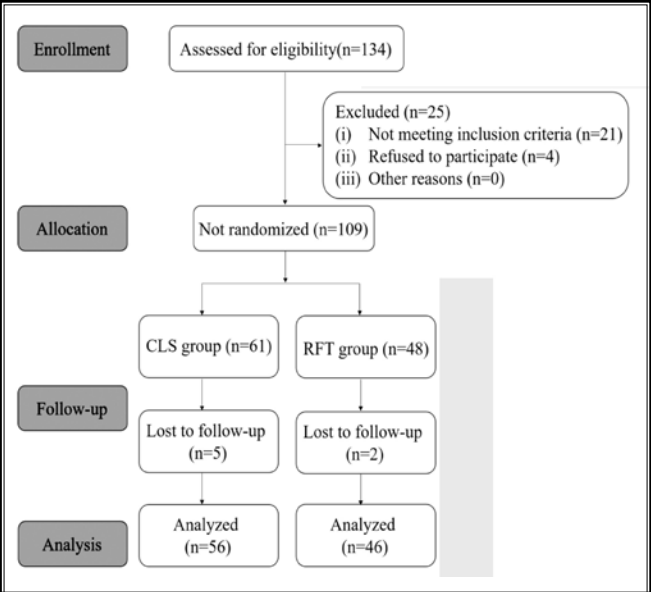

Fig. 3. *Flowchart of study patients.*

Table 1. *Comparison of patient characteristics in the 2 groups.*

Variable	CLS group (n = 56)	RFT group (n = 46)	t/χ^2	*P*
Gender (Male/Female)	16/40	16/30	0.453	0.501
Age (years)	55.48 ± 10.76	54.76 ± 10.79	0.336	0.737
Disease course (months)	73.61 ± 61.12	73.59 ± 67.06	0.002	0.999
Preoperative T	29.39 ± 1.86	29.00 ± 1.65	1.095	0.276
Preoperative PI	1.14 ± 0.59	1.06 ± 0.44	0.696	0.488
Postoperative T	34.58 ± 1.07	33.97 ± 1.98	1.975	0.051
Postoperative PI	7.11 ± 2.81	7.07 ± 2.90	0.077	0.939

CLS, chemical lumbar sympathectomy; RFT, radiofrequency thermocoagulation; T, plantar temperature; PI, perfusion index.

T and PI Before and After Treatment

All patients completed the operation successfully. The T during the before and after treatment of the CLS group was 29.39 ± 1.86 and 34.58 ± 1.07. The T in the before and after treatment of the RFT group was 29.00 ± 1.65 and 33.97 ± 1.98. The T increased significantly postoperatively compared to preoperatively in both groups ($P < 0.05$, Fig. 4A). The PI in the before and after treatment of the CLS group was 1.14 ± 0.59 and 7.11 ± 2.81. The PI in the before and after treatment of the RFT group were 1.06±0.44 and 7.07±2.90. The PI increased significantly postoperatively compared to preoperatively in both groups ($P < 0.05$, Fig. 4B).

VAS Score of CHHF

VAS scores were compared on pre-operation, day 1 and 1 month, 3 months, 6 months, and 1 year after the surgery. Violin plot analysis showed that the VAS scores at 3 months, 6 months, and 1 year after the treatment were significantly lower in the RFT group compared to the CLS group ($P < 0.05$). No significant difference was detected in the VAS score between the 2 groups on pre-operation, day 1, and 1 month after the treatment ($P > 0.05$, Fig. 5).

Effective Rate of Recurrence-free Survival

In the CLS group, recurrence-free survival rates of patients at 1 month, 3 months, 6 months, and 1 year after operation were 92.86%, 76.79%, 67.86%, and 62.50%, respectively. In the RFT group, the recurrence-free survival rates of patients at 1 month, 3 months, 6 months, and 1 year after operation were 97.83%, 95.65%, 86.96%,

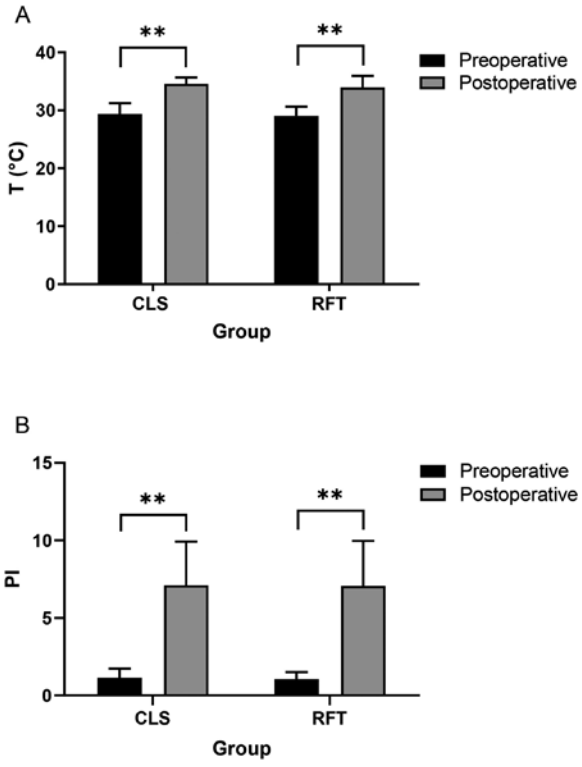

Fig. 4. (A) *Comparison of T in the before and after treatment and* (B) *Comparison of PI in the before and after treatment.*
CLS: chemical lumbar sympathectomy; RFT: radiofrequency thermocoagulation; T: plantar temperature; PI: perfusion index.

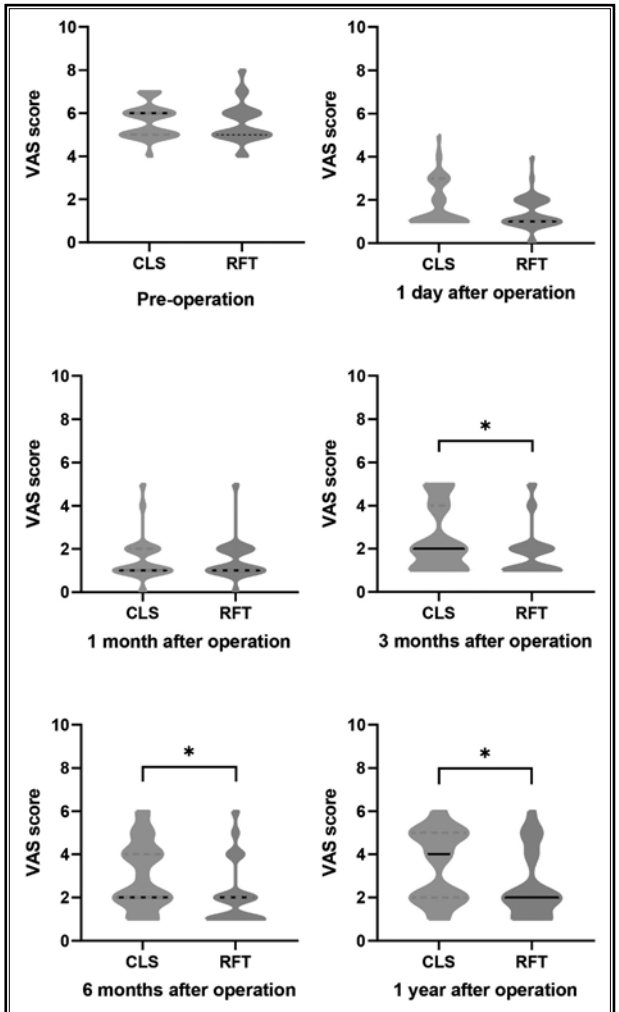

Fig. 5. *The violin plot of VAS scores in the 2 groups.*
CLS: chemical lumbar sympathectomy; RFT: radiofrequency thermocoagulation; VAS: visual analog scale.

and 80.44%, respectively. The Kaplan-Meir curve of recurrence-free survival is shown in Fig. 6. During the 1-year follow-up, patients undergoing CLS had a higher risk of recurrence than those undergoing RFT ($P = 0.036$, log-rank test). The long-term effect of CHHF in the RFT group was better than that in the CLS group.

Postoperative Complications

In the CLS group, 7 (12.5%) patients developed discomfort after treatment. Among them, 3 complained of pain at the puncture point, and the longest course of the disease was 2 months, followed by gradual relief. One case developed hyperhidrosis of the lower extremities and improved for 1 month, and 3 cases developed pain in the groin and thigh region, which disappeared within 1 week. In the RFT group, 3 (6.5%) patients developed postoperative complications, including 2 patients with low back pain and one patient with groin, buttocks, and thigh pain, and the symptoms improved significantly within 1 week. No other adverse events and deaths were observed.

Discussion

CHHF is a disease characterized by abnormal cold, and the lower extremities were the most frequently affected parts. In a study of the correlation between CHHF and health-related quality of life, CHHF has an independent negative effect on the health-related quality of life (10). In this study, we found that the age of patients with CHHF was mainly between 50 and 60 years old, suggesting that the incidence of CHHF may be related to altered hormone levels.

Sympathectomy can be performed in different ways: open surgery, endoscopy, chemistry (phenol or anhydrous ethanol), or radiofrequency. Among these methods, CLS and lumbar sympathetic RFT do not require general anesthesia under endotracheal intubation and are less invasive. Phenol exerts significant damage, giving rise to severe complications of cardiogenic shock and acute renal failure (11,12). Anhydrous ethanol is chosen as the nerve damage agent in our study. In addition, using CT-guided treatment, designing the best puncture path, and implementing the puncture according to the measured depth and angle, we could reduce the number of punctures and improve the success rate of the puncture.

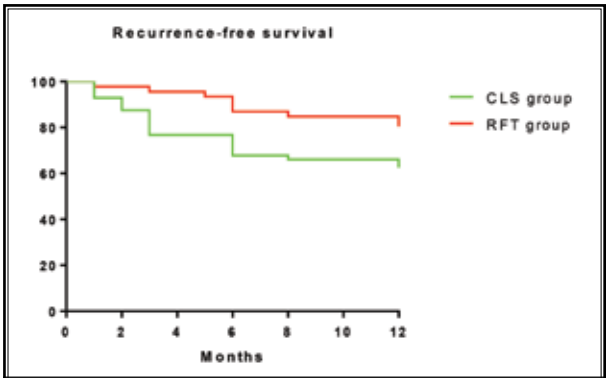

Fig. 6. *Kaplan-Meir analysis of recurrence-free survival.*

Furthermore, owing to its safety, effectiveness, minimal invasiveness, and low cost, percutaneous lumbar sympathectomy has become a primary treatment to improve the blood flow of lower limbs. It also has a good curative effect on refractory diseases, such as recalcitrant erythromelalgia and complex regional pain syndrome (13,14). Radiofrequency can block sensory abnormalities and pain signals transmitted through the sympathetic nervous system. It has a remarkable curative effect in the treatment of Raynaud's disease, trigeminal neuralgia, and limb pain (15-18). In this study, we applied RFT to treat CHHF and compared it to CLS. Overall, the 2 methods for the treatment have achieved satisfactory results. The T and PI were significantly higher, and the VAS scores were significantly lower after the treatment than those before the treatment in both groups. PI is a quantitative value reflecting the real-time change of peripheral blood flow at the monitoring point. It is calculated as the ratio of pulsatile blood flow to non-pulsatile components (other tissues) at the detector site. When the blood flow through the detector site increases, because the non-pulsatile component does not change, the ratio is increased (19). Previous studies have shown that PI can serve as an indicator of successful sympathectomy (20,21). By comparing the PI and T of the 2 groups after treatment, our results suggested that the short-term effects of the 2 minimally invasive procedures in the treatment of CHHF are similar ($P > 0.05$). However, the long-term follow-up results showed that the long-term effect of the RFT group was better than that of the CLS group, and the VAS score in the RFT group was lower than that in the CLS group ($P < 0.05$).

The survival curve suggested that the postoperative recurrence rate in the RFT group was lower than that in the CLS group. The recurrence rates of patients in the CLS and RFT groups were 37.50% and 19.56%, respectively, after treatment for 1 year. The postoperative recurrence is mainly caused by incomplete destruction and regeneration of nerve fibers (7). Herein, we found

a significant difference in the recurrence rate between the 2 groups ($P < 0.05$). This phenomenon could be attributed to the fact that RFT can locate nerves accurately, thus cutting off the nerve completely. However, during the implementation of CLS, the nerve damage depends on the diffusion of drugs, which cannot accurately locate the lumbar sympathetic nerve. In addition, as the effect of the drug fades, the neurological function recovers slowly. Therefore, the recurrence of RFT is less compared to CLS in treatment CHHF. Some patients still relapse after undergoing RFT, which might be because the nerve fibers can be regenerated (22).

The occurrence of adverse events also requires a high degree of vigilance. Genitofemoral neuralgia is one of the most common complications after lumbar sympathetic nerve destruction. CLS uses chemical destruction agents to achieve neurolysis. Through the loss of sympathetic nerve effect, the blood vessels were dilated, and blood perfusion of the lower limbs was increased to relieve the cold sensation in the lower extremities. Although CT-guided puncture reduces complications, the diffusion can accidentally damage the adjacent structures because the damaging agent is fluid, causing injury to the genitofemoral nerve and lateral femoral cutaneous nerve (23). The failure of puncture has the risk of ureteral injury (24). T12 and L1 ganglia play a key role in ejaculation, and the upward spread of the destructive agent can lead to concomitant dysfunction (13,25). In the current treatment, the withdrawal syringe, lidocaine block test, and anhydrous ethanol distribution under CT were confirmed. No severe complications of sexual dysfunction and renal failure were observed. In this study, 3 patients in the CLS group developed genitofemoral neuralgia, which was relieved spontaneously within 1 week. One patient developed hyperhidrosis in the lower extremities 3 months after the operation, which might be related to the recovery of sympathetic nerve function.

The temperature and time of RFT vary with the location of the operation. Wang et al set the temperature of RFT to 95°C for 120 s in the treatment of V1 trigeminal neuralgia (16). In the study of Oh et al, RFT at 80-90°C for 90 s was used to treat intractable chest wall pain (26). In the RFT treatment for coccydynia, the radiofrequency temperature was set at 80°C for 120 s (27). In addition, radiofrequency coagulation was set at 95 °C for 300 s to treat Raynaud's disease (15). The operation range of the exposed end of the radiofrequency needle expands with the increase of temperature. In the present study, the primary purpose of choosing RFT at 95°C for 300 s to treat CHHF is to make nerve damage more complete and improve the long-term effect. However, this might lead to more complications, although no severe complications occurred during the 1-year follow-up. This phenomenon suggested that high temperature and long-time RFT were safe and effective choices, which reduced the postoperative recurrence rate. RFT uses the radiofrequency electrode to destroy the sympathetic nerve through high temperatures, which is accurate and controllable. It could reduce the area of injury and the occurrence of postoperative complications. In this study, only one patient developed genitofemoral neuralgia during a long-term follow-up of 1 year after the operation that improved without intervention, which might be related to the difference in the distance from the genitofemoral nerve to lumbar sympathetic trunk among different individuals. Previous studies have shown that the distance from the genitofemoral nerve to the lumbar sympathetic trunk is 0-28 mm at the level of L3/4, and some of it was < 5 mm (28). Therefore, lumbar sympathectomy can easily damage the genitofemoral nerve, especially in patients undergoing CLS.

Compared to CT, MRI is advantageous to the tissue as it locates the lumbar sympathetic trunk accurately. The injury of the genitofemoral nerve and lateral femoral cutaneous nerve can be reduced (29). However, the clinical application of MRI is still limited because of the high cost, shortage of equipment, and lack of contact with metal substances.

Nevertheless, the present study has some limitations. Firstly, the small sample size and short follow-up time may lead to bias. Secondly, this was a retrospective, nonrandom, single-center study. During the follow-up period, the VAS scores of patients may be biased due to different environmental temperatures. Thus, prospective, randomized, and multicenter trials with large sample sizes are required to substantiate the current results.

Conclusions

In conclusion, our study suggested that RFT had better long-term efficacy, fewer complications, and lower relapse than CLS in the treatment of CHHF. RFT is a better treatment option for CHHF.

Authors Contributions

JCT and MY designed the study. JCT wrote the manuscript. JYT and GL collected the data. JJZ and QLH performed the data analysis. HDN, KYX, BH, and MY reviewed the final draft. All authors read and approved the final manuscript. MY is responsible for this article.

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