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## ORIGINAL ARTICLE

Prostate Disease

# Transrectal microwave thermotherapy causing a short-time influence on sperm quality in Chinese chronic nonbacterial prostatitis patients

Jia-Xin Jin<sup>1,\*</sup>, Han-Zhang Wang<sup>2,\*</sup>, Zheng-Xing Zhai<sup>1</sup>, Bao-Liang Ma<sup>1</sup>, Qin-Fang Li<sup>1</sup>, Nan Xiao<sup>1</sup>, Zhi-Ping Wang<sup>1</sup>, Ronald Rodriguez<sup>2</sup>

Chronic prostatitis can affect the sperm's quality. Previous studies have shown that transrectal microwave thermotherapy (TRMT) results in symptomatic relief in patients with chronic prostatitis, but the effects on sperm have not been carefully investigated. This study evaluates the impact of TRMT on the relief or decrease of symptoms and quality of sperm when used to treat patients with chronic nonbacterial prostatitis. Sixty patients were enrolled in the study. TRMT treatment was administered over 5 days, 1 h per day. Semen examination was carried out pretreatment and immediately at the conclusion of the 5-day treatment. Also, it was repeated 1 month, 3 months, and 6 months later. The treatment's symptom relief efficacy was evaluated using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI). After the treatment, the overall NIH-CPSI scores were lower compared to those of pretreatment. In addition, the white blood cells and lecithin in expressed prostatic secretion were normal after the treatment. The sperm count was decreased by 23.8% 3 months after the treatment, sperm motility was reduced by 10.3% immediately after treatment, and sperm deformity was increased by 17.2%. The sperm volume and PH were not affected. However, the sperm quality recovered after treatment and the malformation rate was also lower at 6 months after treatment. TRMT is a favorable and safe treatment option for patients with nonbacterial chronic prostatitis. It could relieve the patient's symptoms and impact on sperm quality in the short-term.

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## INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common disease among men and accounts for approximately 9.0%–16.0% of urology outpatients.<sup>1</sup> Symptoms include pelvic pain localized to the prostate, perineum, or urethra, and varying degrees of voiding and sexual dysfunction.<sup>2</sup> The NIH International Collaborative Prostatitis Network developed a prostatitis classification system in 1995,<sup>3</sup> which defined CP/CPPS as Category III prostatitis characterized by its nonbacterial nature with or without prostatic inflammation. Although a variety of pharmacologic and nonpharmacologic therapies have been used to treat CP/CPPS, most have shown poor efficacy because the pathogenesis of CP/CPPS is still unclear.<sup>4</sup> In the 1990s, microwave thermotherapy was used to treat CP/CPPS, and other research suggests microwave thermotherapy to be more effective than any other method.<sup>5</sup> Studies have shown that 50.2% of patients' symptoms are improved and 67.1% of patients experienced totally pain relief.<sup>6</sup>

There are two methods of microwave thermotherapy to treat chronic prostatitis: Transurethral Microwave Thermotherapy (TUMT)

and Transrectal Microwave Therapy (TRMT), both of which have advantages and disadvantages. While TUMT has better efficacy,<sup>7</sup> it is an invasive procedure, often causing the patient discomfort, urinary tract infections, and even urethral injury.<sup>8</sup> Compared to TUMT, TRMT is easier for patients to tolerate and posttreatment is associated with the incidence of lower urinary tract infections.<sup>9</sup>

In our previous studies, we found that the relative efficacy for CP/CPPS patients who were treated with medication, TRMT, or a combination of medication and TRMT was 54.5%, 69.8%, and 80.8%, respectively.<sup>10</sup> Patients also exhibited lower posttreatment NIH-CPSI scores relative to pretreatment ( $P < 0.01$ ).<sup>10</sup> Based on the above data, TRMT is considered an effective treatment for CP/CPPS.

Although TRMT is an effective treatment for CP/CPPS, little is known about its impact on semen quality. Given that TRMT delivers high levels of heat to the pelvic floor and prostate, we considered the possibility that TRMT may acutely harm the sperm stored in that area. We investigated whether heat and electromagnetic radiation delivered by TRMT may adversely affect sperm acutely.

<sup>1</sup>Institute of Urology, Department of Urology, Key Laboratory of Diseases of Urological System Gansu Province, Gansu Nephro-Urological Clinical Center, Lanzhou University Second Hospital, The Second Clinical Medical College of Lanzhou University, Lanzhou 730000, China; <sup>2</sup>Department of Urology, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, Texas 78229-3900, USA.

\*These authors contributed equally to this work.

Correspondence: Dr. ZP Wang (eywzp@lzu.edu.cn)

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## PATIENTS AND METHODS

Patients were collected from one center (Department of Urology, Lanzhou University Second Hospital) between March 16, 2013, and November 10, 2014. The study is a retrospective cohort study. There is no control group for the study, and we used self-control method to compare the treatment efficacy and sperm quality from pretreatment, posttreatment, and follow-up examination. The study approval was given by the Medical Ethics Committee of the Second Hospital of Lanzhou University using standardized IRB consent processes for the institution.

We sequentially collected sixty patients, whose age ranged from 20 to 60 years (mean age 35.7 years) with a history of CP/CPPS for 3–120 months (median of 20 months). The patient's main symptom was documented with 27 patients reporting pelvic pain, nine patients had voiding dysfunction, and 24 patients had anxiety and depression. The patients were divided into two groups: 20–40-year-old (43 cases) and 40–60-year-old (17 cases). In each group, the patients were classified into two subgroups - IIIA (37 cases) and IIIB (23 cases) - according to the NIH prostatitis classification and patient history, physical examination, urinalysis, and expressed prostatic secretion test (EPS) (**Table 1**).

### Patients' enrollment

Patients who were enrolled in the study should fit for the following diagnostic process. Patients with the main complaints such as pain in the pelvic region or belly of the scrotum, or abnormal urination, were examined further. A digital rectal examination was performed to confirm prostate size and determine the presence of tenderness or nodules on the prostate. If the patients have the above symptoms and the digital rectal examination showed there is some pathological changes on the prostate, then they have to take a urinalysis to make sure whether there are bacteria, also need an expressed prostatic secretion (EPS) test. The WBC (>10/HP) and/or the EPS result (decreased lecithin count) were determined if the patient met the NIH classification for CP/CPPS Type IIIA (inflammatory) or IIIB (noninflammatory). Every patient completed an NIH-CPSI.

Because it is not known whether the heat used in the therapy would injure sperm, patients who were unmarried or had no children were excluded. Patients who received previous treatments for CP/CPPS were excluded to ensure that any abnormal sperm finding was not influenced by previous treatments. Differential diagnostic procedures were used to eliminate other diseases that could cause pelvic pain, such as cystitis or anorectal phlogistic diseases<sup>11</sup> (**Figure 1**).

### Transrectal microwave thermotherapy

Patients included in the study were treated with TRMT for 1 h daily for 5 days with the ZRL-II-A Cavity Intervention Therapy Instrument (Shanghai Songhang Industry, Co. Ltd., Shanghai, China). The treatment temperature was controlled at 41–42°C.

### Efficacy assessment and Semen examination

Patients completed the NIH-CPSI and underwent an EPS examination before and after the TRMT 5-day treatment to evaluate the therapeutic efficacy, and NIH-CPSI survey was repeated at first month, 3 months, and 6 months after the treatment to consider the long-time efficacy. The

**Table 1: Patients data**

Age (year)	Subgroup		Total
	IIIA	IIIB	
20–40	28	15	43
40–60	9	8	17
Total	37	23	60

nine-question NIH-CPSI addresses four separate aspects of CP: pain or discomfort, urination, impact of symptoms, and quality of life. The tool categorizes the responses into three domains: pain, urinary symptoms, and quality of life impact. To evaluate the severity of the CP/CPPS, the pain and urinary symptom domain scores are combined. A score of 0–9 is considered mild, 10–18 as moderate, and 19–31 as severe.

Seminal tests were performed immediately before and after the TRMT treatment. Subsequent tests were performed at the first month, third month, and sixth month after therapy. Patients used a private room near the laboratory to collect semen samples. Instructions were given to wash their glans penis with soap and water. After urinating, samples were obtained by masturbation and ejaculated into a sterile collection tube. The semen was incubated at 37°C for 25–45 min for liquefaction. Semen examination was performed using an Automatic Sperm Quality Analyzer (CASAS-QH-111 Tsinghua Tong Fang Co., Ltd., Beijing, China). The sperm count, sperm density, motility rate, percentage of Grade A + Grade B sperm (fast forward movement plus slow forward movement), the morphologically abnormal percentage, the semen volume, and PH were evaluated.

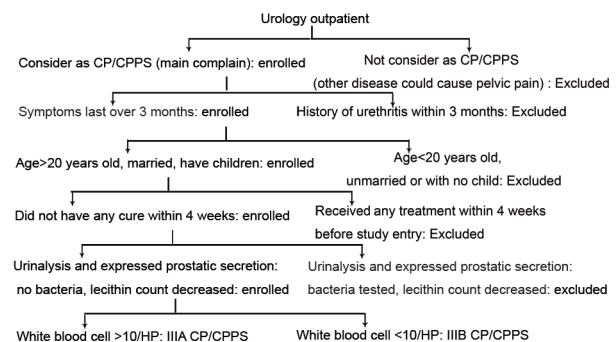
### Statistical analysis

All results are average values  $\pm$  standard deviation and analyzed using Excel® 2013 (version Office 2013 home for Windows, Microsoft Co., Redmond, WA, USA). Correlations among variables were calculated using Spearman's rank correlation coefficient with statistical software SPSS (version 22.0 for Windows, SPSS Inc., Chicago, IL, USA).  $P < 0.05$  was considered statistically difference. Because the amount of the cohort group is small, and all patients' sperm quality is among the normal range, there would no significant difference or some difference missed.

## RESULTS

Patients entered the follow-up phase of the study at the conclusion of TRMT therapy. After the 6-month semen test and the completion of the questionnaire by the study participants, all data were analyzed to examine the sperm quality, NIH-CPSI scores, and the correlation between the two datasets.

Comparing pretreatment and immediate posttreatment data, sperm count, sperm density, sperm motility, and Grade A + Grade B sperm rate were all decreased after the TRMT treatment (**Table 2**). The sperm count was decreased by 23.8% ( $P < 0.05$ ) and sperm density was decreased by 25.1% ( $P < 0.05$ ). Sperm count and density returned to pretreatment levels at 3 months posttreatment. The abnormal sperm morphology was increased by 17.2% immediately after therapy ( $P < 0.05$ ) but decreased by the first month after treatment. The high-frequency microwaves used during TRMT influence sperm viability and sperm motility which was reduced by



**Figure 1: Patient enrollment criteria.**



**Table 2: Sperm quality test results (n=60) ( $\bar{x}\pm\sigma$ )**

Test time	Sperm count (million)	Sperm density (million ml <sup>-1</sup> )	Sperm motility (%)	Grade A+Grade B rate (%)	Abnormality rate (%)	pH	Volume (ml)
Pretreatment	213.28±2.24	123.44±1.15	75.91±0.20	63.80±0.23	17.78±0.11	7.38±0.00	4.56±0.01
Immediate posttreatment	162.57±1.65*	98.64±0.69*	68.52±0.19*	56.97±0.17*	20.84±0.09*	7.44±0.01	4.62±0.02
1 month posttreatment	176.75±1.69	109.34±0.76	72.10±0.18	60.19±0.17	17.80±0.08*	7.43±0.00	4.55±0.01
3 months posttreatment	201.40±1.96	122.50±0.89 <sup>^</sup>	75.43±0.19 <sup>^</sup>	62.58±0.19 <sup>^</sup>	16.10±0.07	7.40±0.00	4.67±0.01
6 months posttreatment	209.85±2.00 <sup>§</sup>	129.54±0.96 <sup>§</sup>	77.47±0.18 <sup>§</sup>	63.98±0.20 <sup>§</sup>	15.38±0.07*	7.44±0.00	4.72±0.01

Sperm quality parameters results at five intervals - pretreatment, immediate posttreatment, and 1-, 3-, and 6-month posttreatment. \* $P < 0.05$  between pretreatment and immediately after treatment/first month; <sup>^</sup> $P < 0.05$  between immediate posttreatment and 3 months posttreatment; <sup>§</sup> $P < 0.05$  between immediate posttreatment and 6 months posttreatment

10.3% after treatment ( $P < 0.05$ ) but recovered by the third month posttreatment. However, there is not much difference in both semen volume and PH among pretreatment, posttreatment, and the follow-up data. Sperm quality was also affected by the patient's age and types of CP/CPPS (IIIA/IIIB).

We have made the sperm test results of pretreatment as 100.0%, and then compared the coming sperm test results with pretreatment results to know the percent change of sperm quality. In patients aged 20–40 years, sperm count, sperm density, and rate of Grade A + Grade B sperm exhibited an uptrend 6 months after treatment (**Figure 2a**). The TRMT impact is less for patients aged 40–60 years than for aged 20–40 years (**Figure 2b**). Compared the data from patients as the same age of 20–40 years with different type of CP/CPPS. For patients with Type IIIA (**Figure 3a**), The percentage of sperm motility, rate of Grade A + Grade B sperm, and normal sperm rate is lower than pretreatment measurements, but with an upward trend by the end of the study. Because of follow-up limitations, it is unclear whether the uptrend would have continued beyond the pretreatment data. A rising trend is seen in sperm motility for patients with Type IIIB CP/CPPS by the end of the study (**Figure 3b**). Except for the sperm count, all other study parameters were higher at the sixth month posttreatment examination than pretreatment. In patients aged 40–60 years (**Figure 3c and 3d**), the results for patients with IIIB CP/CPPS demonstrated a rising trend for all parameters except for normal sperm rate. For patients with IIIA CP/CPPS, only sperm motility and Grade A + Grade B sperm rate demonstrated an uptrend.

We found that TRMT decreased sperm quality for patients with IIIA CP/CPPS at the age of 40–60 years at a greater incidence than at the age of 20–40 years (**Figure 3**). The sperm count, density, and Grade A + Grade B sperm trended upward in sperm quality at the sixth month posttreatment for the younger patient group (**Figure 3a**). Sperm quality was decreased immediately for patients aged 40–60 years with IIIB CP/CPPS, but a lasting effect was not evident at the sixth month after treatment.

#### Treatment effect on NIH-CPSI score and EPS examination

Except for pretreatment and posttreatment survey, we also obtained follow-up NIH-CPSI questionnaires from all patients to measure the efficacy of the treatment based on their symptoms and pain. Forty-six patients reported a decrease in symptoms, nine patients reported their symptoms as moderate, and the rest of six patients' symptoms persisted. The overall NIH-CPSI scores of all patients were meaningfully different than pretreatment scores ( $P < 0.05$ ) (**Table 3**). Examination of the patients' EPS results indicated the lecithin content recovered to normal levels in 53 patients and in 22 patients with IIIA prostatitis. The number of white blood cells returned to the mean of 0–2/HPE.

#### The correlation analysis

The correlation analysis showed that there was a positive correlation between sperm abnormality and NIH-CPSI ( $r = 0.04082$ ,  $P < 0.05$ )

(**Figure 4**), but there was no positive or negative correlation between other data and NIH-CPSI score ( $P > 0.05$ , data not shown).

## DISCUSSION

Chronic prostatitis (CP) is regarded as a multifactorial complex of symptoms. The standard treatment method is antibiotics, but due to the special structure and situation of prostate, antibiotic treatment does not show a better efficacy. In chronic pelvic pain syndrome (CPPS), the pathology is not very clear and there is no standard therapy guideline. Antibiotics, anti-inflammatory drugs, and phototherapeutics are used as treatment options. All methods show unsatisfactory efficacy on CP/CPPS.<sup>12</sup> Although some studies showed a good result for TRMT treat with CP/CPPS, this treatment has not gained wide acceptance, and there are still some controversies.<sup>13</sup> However, transurethral thermotherapy caused some adverse effects, such as urinary tract infection, hematuria, and pain.<sup>14</sup> Based on the above statement, transrectal thermotherapy became a promising treatment for CP/CPPS because few side effects have been showed. Some trials included patients diagnosed with CP/CPPS and NIH-CPSI scores  $>8$  to receive TRMT treatment. Signs and symptoms were relieved to varying degrees in 50.2% of the patients.<sup>6</sup> In our previous studies, we found the relative efficacy for CP/CPPS patients who were treated with medication, TRMT, or a combination of medication and TRMT was 54.5%, 69.8%, and 80.8%, respectively. After treatment, the overall NIH-CPSI of the three groups was different than pretreatment ( $P < 0.01$ ).<sup>10</sup> As a result, TRMT is a promising method of treatment for CP/CPPS. The therapeutic mechanism of TRMT is heat caused by microwaves, which improves the blood circulation of the prostate gland. We concluded that the treatment would improve the local metabolism of the prostate, thereby boosting auto-immunity reflection and promoting inflammation dissipation. The heat could reduce the excitement of pelvic sensory neurons, resulting in decreased prostate muscular tension.<sup>15</sup>

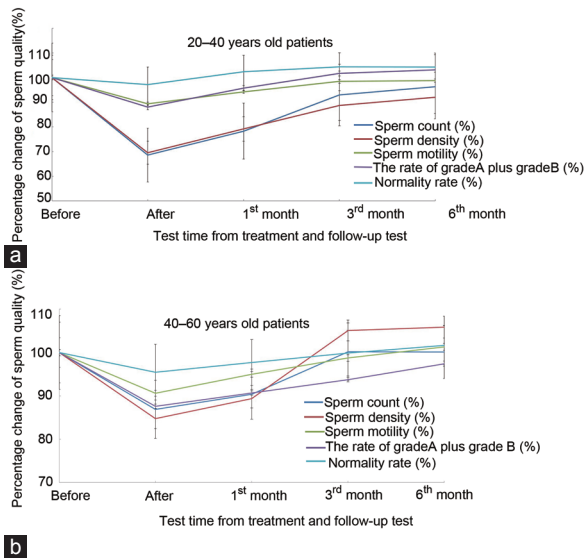
Semen is primarily composed of two separate components: sperm and seminal plasma. The seminal plasma's composition is prostatic secretion, seminal vesicle fluid, and secretion of bulbourethral gland.<sup>12</sup> Therefore, CP/CPPS could affect the semen as well. Jung and Schuppe<sup>16</sup> found that the genial heat stress could affect the sperm quality. Our study showed that TRMT hurt the sperm for short-time effects. We used computer-assisted sperm analysis (CASA) to test the sperm quality. Although manual sperm analysis is thought more accurate than CASA, CASA is more acceptable in clinical with the software and technology development,<sup>17–19</sup> such as sperm concentration and motility, especially for the morphology of sperm.<sup>20</sup>

Hallin *et al.*<sup>5</sup> found that there are no statistically significant differences for sperm quality between pre- and post-TUMT immediately, regarding semen emission (semen volume, total sperm number, total fructose, and zinc) or sperm morphology. In

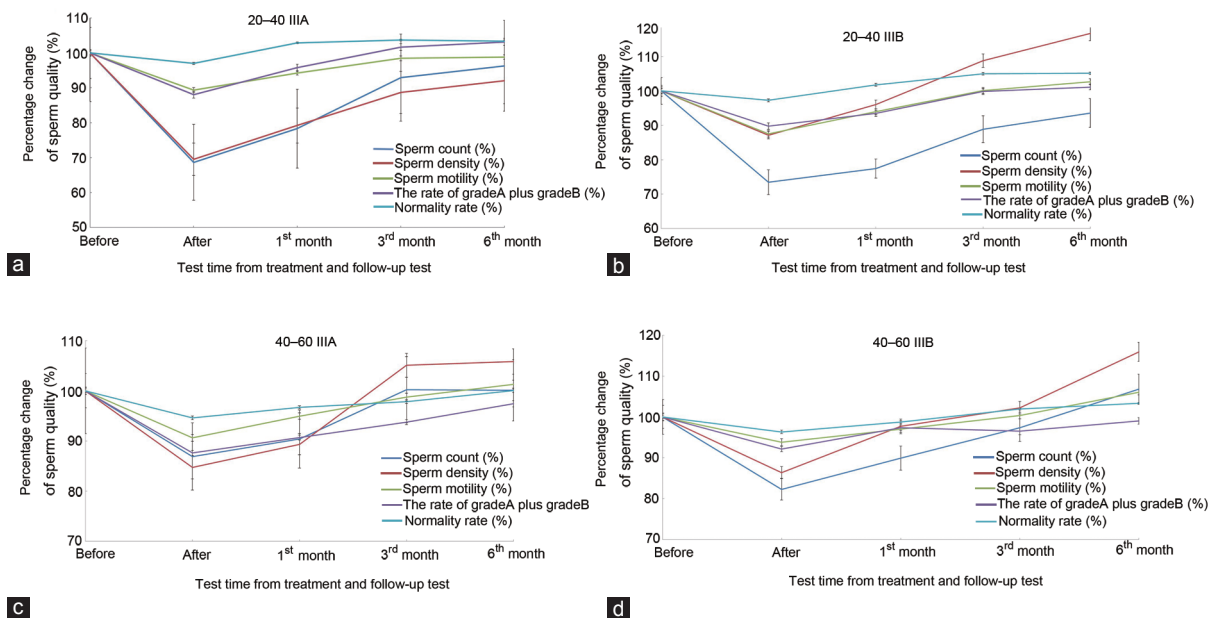
contrast, we found that there is a short-time adverse effect on sperm. A semen examination at the end of the 5-day therapy showed sperm quality declined, indicating that TRMT could be an obstacle in the development and maturation of sperm. However, sperm quality improved by the first month after therapy and gradually improved in subsequent examinations. Some semen quality parameters in the sixth month posttreatment equaled pretreatment results. The study

outcome indicated that microwaves could negatively affect sperm during the treatment. Sperm count decreased 23.8%, and sperm density was reduced as well immediately after treatment. Sperm count and density returned to pretreatment's level 3 months after treatment. As high-frequency microwaves influence the sperm vitality, motility was reduced 10.3% immediately posttreatment, but returned to normal by the third month after treatment. The sperm deformity rate was increased 17.2%. The abnormal rate of sperm decreased the first month after treatment, and malformation rates were significantly lower by the sixth month after treatment. As it takes 3 months for spermatogonial cells to develop into mature and functionally sperm in most men, patients receiving TRMT should have sperm examinations in the third and sixth month after the treatment to evaluate any side effects. Nevertheless, long-term side effects on sperm from the treatment were not evident in this study. From the correlation analysis, we found that the sperm abnormal rate has a positive correlation with NIH-CPSI score ( $P < 0.05$ ), no literature and studies clarify this, we cannot conclude that if the patient's symptom is severe would cause the sperm have a higher abnormal rate. From our study, every patient's sperm quality is above the normal range, even after the TRMT treatment immediately, also from the follow-up test results. Based on those reasons, we cannot say that whether the patient feels much more painful would have a positive effect on sperm abnormal rate. This should have a further study to confirm this result.

Although TRMT treatment affects sperm in the short-term, it did not have the same effect on patients with different age and CP type. Because the sperm quality would be affected by the age and the time course of CP, the elder patient or the patient suffer from CP/CPPS with a long-time could have lower sperm quality. Menkveld *et al.*<sup>21</sup> indicated that IIIA CP/CPPS has a significant negative effect on sperm morphology parameters, but IIIB CP/CPPS has not much



**Figure 2:** Changes of sperm quality for (a) age of 20-40 years', (b) age of 40-60 years' patients at different test time point (the sperm results of before treatment as 100.0%).

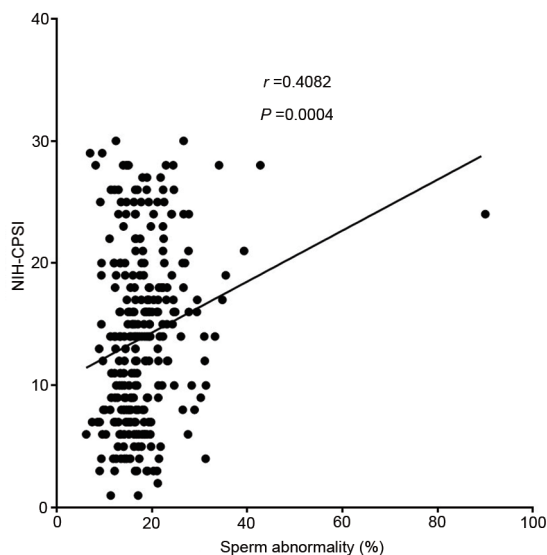


**Figure 3:** (a) Changes of sperm quality for age of 20-40 years' patients with IIIA CP/CPPS at different test time point (the sperm results of before treatment as 100.0%); (b) changes of sperm quality for age of 20-40 years' patients with IIIB CP/CPPS at different test time point (the sperm results of before treatment as 100.0%); (c) changes of sperm quality for age of 40-60 years' patients with IIIA CP/CPPS at different test time point (the sperm results of before treatment as 100.0%); (d) changes of sperm quality for age of 40-60 years' patients with IIIB CP/CPPS at different test time point (the sperm results of before treatment as 100.0%).

**Table 3: NIH-CPSI changes (n=60) ( $\bar{x}\pm\sigma$ )**

Subgroups	Age (years)			
	20–40		40–60	
	IIIA prostatitis	IIIB prostatitis	IIIA prostatitis	IIIB prostatitis
Pretreatment	24.91±4.30	21.74±3.67	17.86±6.44	20.06±2.37
Posttreatment	16.79±2.15*	12.11±5.23*	10.54±3.83*	14.48±4.92*
1 month posttreatment	12.34±3.26*	11.89±2.54*	11.25±4.55*	12.75±3.71*
3 months posttreatment	7.95±2.21*	9.56±3.11*	9.69±2.04*	10.20±2.68*
6 months posttreatment	7.31±1.52*	6.82±1.84*	8.97±1.85*	9.96±3.34*

\* $P<0.05$  between pretreatment and after treatment. NIH-CPSI: national Institutes of Health Chronic Prostatitis Symptom Index

**Figure 4:** Correlation of sperm abnormality with NIH-CPSI scores.

effect sperm. In our research, the TRMT impact is less in patients with age 40–60 years than 20–40 years. For different type of CP/CPSPS, present data indicate that efficacy on sperm quality with TRMT treatment is superior in patients with IIIB CP/CPSPS than with IIIA CP/CPSPS. Because of this retrospective study, we did not test the semen reactive oxygen species (ROS). However, in our previous study, we found TRMT could decrease ROS in semen and prostate fluid in the patient after the treatment which is also an important factor for sperm quality.<sup>10</sup>

TRMT could have an effect on CP/CPSPS from the results of previous studies and the present study. The patient's symptoms were eased after the treatment, and NIH-CPSI was decreased at the end of the treatment and follow-up. Therefore, TRMT is a promising treatment of CP/CPSPS in the future. According to the guide book of TRMT, it is not applicable for all CP/CPSPS patients, especially for patients who are unmarried or who plan on a child in the near future. Nonetheless, our study showed that TRMT could not inhibit the sperm quality in a long-time period. We should control the time and temperature of therapy to decrease any side effect and increase the treatment safety for all patients.

In this study, because the patients only received one course of TRMT treatment and the follow-up period was limited to 6 months, we did not know whether this treatment could cause long-term

effects on the quality of sperm and the degree of side effects. Furthermore, we need add other semen tests, such as sperm DNA damage rate and ROS level to confirm this treatment could not hurt the sperm in a long-time course. Besides, because this study was a retrospective study, there was no control group to compare with, and the number of patients is not as many as possible, based on these reasons, it showed a potential limitation to give us a further answer about this side-effect on sperm quality from TRMT treatment. We will continue further research to determine any long-term effects caused by TRMT and provide a better guide for this treatment with lower side effects.

## CONCLUSION

Our study reveals TRMT may be an effective therapy for Type III CP/CPSPS. The efficacy showed there is good for patient's symptom relief. There is a short-time negative change for sperm quality caused by TRMT, compared with pretreatment results, but all data showed that sperm quality returned to the baseline. Based on the present study, we conclude that the TRMT treatment did not influence the sperm quality for a long-time period, and is a promising treatment for CP/CPSPS.

## AUTHOR CONTRIBUTIONS

JXJ participated in designing the study, collected the data, the proteomic analysis, and drafted the manuscript. HZW involved in its design and helped draft and revise the manuscript. ZXZ performed the statistical analysis. BLM and QFL contributed to the treatment for patients and sample analysis. NX participated in manuscript revised. ZPW and RR supervised the research and revised the manuscript. All authors agreed and approved the final manuscript.

## COMPETING INTERESTS

All authors declared no competing interests.

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