ELSEVIER

HEAT THERAPY IN THE TREATMENT OF PROSTATITIS

SCOTT I. ZEITLIN

ABSTRACT

There is a dearth of literature on heat therapy and prostatitis. The therapies used different energy sources, including interstitial heat and microwaves, and were delivered both transrectally and transurethrally. Most data precede our present system of nomenclature and therefore are difficult to compare, even with the literature of their day. Validated instruments were rarely used to determine efficacy, and most outcome measures were subjective. We will need well-designed prospective clinical trials using objective outcome measures and validated symptom indexes. Until then the use of heat therapy for prostatitis should be considered experimental. UROLOGY **60:** 38–41, 2002. © 2002, Elsevier Science Inc.

The data on heat therapy for the treatment of chronic prostatitis (CP) are inconsistent with regard to outcome measures, modalities of treatment, and study design. The therapy has been delivered with interstitial heat and microwaves, both transrectally and transurethrally. The power settings and target temperatures are not consistent, and this makes it more difficult to compare the treatments and to evaluate their success. Universally, these studies were done in patients variously described as having nonbacterial prostatitis (NBP) or prostatodynia. These patients would now be classified as National Institutes of Health (NIH) categories IIIA and IIIB.

Target temperatures vary with regard to treatment and therefore with regard to efficacy and number of treatments. Hyperthermia and thermotherapy are distinguished primarily by their target temperature ranges, generally 42° to 44°C for hyperthermia contrasted with temperatures of 45° to 50°C for thermotherapy. With target temperatures >45°C, only 1 procedure is typically performed per patient. The transrectal studies, reviewed below, report temperatures of 41° to 45°C, as do the transurethral microwave hyperthermia procedures. The transurethral microwave thermotherapy (TUMT) procedures have reported temperatures of 45° to 60°C, as do the transurethral needle ablation (TUNA) procedures.

From the Department of Urology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California, USA

Reprint requests: Scott I. Zeitlin, MD, University of California Los Angeles School of Medicine, Department of Urology, 66-131 CHS, Los Angeles, California 90095. E-mail: szeitlin@ucla.edu

TRANSRECTAL HYPERTHERMIA

Servadio *et al.*[1] treated patients with both benign and malignant diseases of the prostate with a transrectal microwave. Altogether, 21 patients with CP (no control subjects) were treated with 6 to 10 treatments consisting of 60 minutes of therapy with target temperatures of 41° to 45°C using a 915 MHz microwave power source. Total follow-up time was 24 months. There were 2 initial patients treated for prostate cancer who developed prostatorectal fistulae; both were treated conservatively. Outcome measures were subjective, and a 28% decrease in symptom parameters was reported. The investigators did not report whether these improvements were clinically and/or statistically significant.

Rigatti *et al.*[2] studied the effects of the same transrectal microwave system used by Servadio *et al.*[1] mentioned above. They evaluated 14 men with NBP to determine whether the treatments had an effect on fertility. Before and after 4 weekly 1-hour treatments, sperm morphology, motility, and count, as well as zinc, citrate, fructose, and free testosterone, were measured. There were no differences noted. They concluded that the treatment could be used safely in men who wanted to preserve their ability to reproduce.

Servadio and Lieb[3] followed this with a larger trial consisting of 45 patients serving as their own controls. A self-administered questionnaire was used to assess subjective symptoms. The patients were treated with 6 weekly sessions, each lasting an hour. Almost half (47.5%) of the patients improved subjectively; 11 of the 45 had complete improvement (defined as 80% to 100% and requiring

0090-4295/02/$22.00
PII S0090-4295(02)02385-3

no further therapy). They were observed an average of 34 months. In all, 21 of the 45 had partial improvement (20% to 75% improvement) and 11 had no improvement (defined as 0% to 10%). Only 5 of the 12 patients biopsied before treatment had histologic evidence of inflammation, and almost all the inflammation was resolved after treatment. In addition, they attribute 5 postprocedure pregnancies to the improvements in semen analysis but do not reveal what these changes were. They conclude that heat may be used on its own or with antibiotics and anti-inflammatories.

Shah *et al.*[4] reported on 30 patients treated with transrectal microwave hyperthermia. This was a placebo-controlled trial with a sham group. The patients had 4 weekly treatments for 1 hour. The abstract did not indicate how many patients had chronic NBP and how many had prostatodynia (now known as category III chronic prostatitis/chronic pelvic pain syndrome [CP/CPPS]. Altogether, 55% of the patients had a >50% reduction in their subjective symptoms carried out to 3 months, and there was a 10% placebo effect.

Montorsi *et al.*[5] reported on 54 patients with NBP and prostatodynia (ie, CP/CPPS) who underwent 1 of 3 protocols of transrectal microwave thermotherapy. Their prostate temperature was the same as the group in Servadio *et al.*, 42.5°C. The patients had 1 of the following treatment regimens: (1) 1 session per week for 4 weeks, (2) 1 session per week for 6 weeks, or (3) 2 sessions per week for 3 weeks. The mean follow-up time was 26 months. Complications included catheter-induced minor hematuria, urinary tract infection (2 of 54, 3.7%), epididymitis (1 of 54, 1.8%), and hematospermia (1 of 54, 1.8%). Long-term follow-up evaluation was available for 44 of 54 patients. They used a modified benign prostatic hyperplasia (BPH) symptom index: 10% to 30% had marked improvement and 30% to 40% had moderate improvement. There was no significant difference with regard to treatment arm. When looking strictly at the long-term outcome, the tendency to improve and consider oneself better occurred with 6 versus 4 treatments and with a week in between treatments.

TRANSURETHRAL HYPERTHERMIA

Baert *et al.*[6] evaluated 15 patients treated with 5 weekly treatments of microwave hyperthermia. Of the 15 patients, 4 (27%) had complete pain relief, and the response tended to be better in patients without "psychological problems" and when the temperatures achieved were higher than 45°C. The patients were observed for only 6 months, and no uniform symptom index was used to collect their data in this phase 1 clinical trial.

TRANSURETHRAL THERMOTHERAPY

With the limited success of microwave therapy for NBP, the focus of thermotherapy changed to a transurethral approach because higher target temperatures could be achieved. Nickel and Sorenson[7] reported on 24 patients treated with the TUMT procedure: 19 with NBP and 5 with prostatodynia (now CP/CPPS). The patients were evaluated with a symptom severity score that consisted of 10 symptoms, including (1) penoscrotal pain, (2) perineal pain, (3) suprapubic pain, (4) painful ejaculation, (5) painful rectal examination, (6) low back, upper leg, or groin pain, (7) stranguria, (8) frequency, (9) urgency, and (10) dysuria. The patients had to score ≥5 on 3 of the 10 symptoms to be eligible for the TUMT procedure. The TUMT procedure was done once for 1 hour. The patients were then evaluated at 3 months with regard to cultures, digital rectal examination, and symptom severity. In the NBP group, 47% had a marked improvement (75% symptom reduction) and 16% had moderate improvement (25% to 75% symptom reduction); 37% were no better. At 3 months, 6 NBP patients thought they were cured, 1 relapsed at 4 months, and 1 additional patient felt cured at 6 months. Only 1 of the 5 patients with prostatodynia had a marked improvement, and all 5 felt the procedure was very uncomfortable. In the NBP group, 5 patients had ≥1 of the following adverse events: (1) hematuria, (2) urinary retention, (3) transient incontinence, (4) impotence or premature ejaculation, (5) urinary tract infection, or (6) epididymitis. Nickel and Sorenson[7] postulated that either the heat accelerates the natural resolution of inflammation or the afferent nerve fibers of the prostate are altered. The only prostatodynia patient who improved was thought to be an NBP patient, and the investigators believed that prostatodynia should not be treated with TUMT at all.

Choi *et al.*[8] evaluated 78 patients (61 NBP, 17 prostatodynia) in a phase 2 trial. They underwent a single 1-hour TUMT session. The patients were observed for 1 year. No placebo group was included and no standardized symptom index was used. Complications included 1 case of epididymitis and 1 case of low-volume ejaculate. A subjective 66% response rate was noted for prostatitis and 76% for prostatodynia at 1-year follow-up evaluation.

Nickel and Sorenson[9] followed their 1994 pilot study with a double-blind study of 20 patients randomized to receive TUMT versus sham therapy. Target temperatures were 45° to 60°C. At 20 months, 70% (7 of 10) of the treatment group responded with a durable response. The investigators concluded that the patients tended to have an increase in inflammation after the procedure,

which confounded their analysis. The data were promising and warranted further studies.

Glass *et al.*[10] reported on 67 patients treated for BPH with TUMT; 1 of the patients went on to develop CP as a consequence of the therapy.

THE HOT BALLOON

Nickel *et al.*[11] studied the combined effects of radiofrequency thermal therapy and balloon dilation of the prostate. They evaluated 5 patients, and although there was some freedom from symptoms at 3 months, only 1 patient remained asymptomatic at 6 months, and no patients were asymptomatic at 9 months. Adverse events included (1) urinary retention, (2) retrograde ejaculation, (3) hematuria, (4) urethral stricture, and (5) worsening of symptoms.

TRANSURETHRAL NEEDLE ABLATION

There have been 2 studies that have looked at the TUNA procedure for the treatment of prostatitis. Chiang *et al.*[12] published a pilot study looking at 7 patients, who were observed for an average of 8 months. Findings showed that 4 patients had a complete response and 3 had a partial response. Lee *et al.*[13] treated 42 patients with NBP with the TUNA procedure and used subjective symptoms for the outcome as well as expressed prostatic secretions white blood cell counts. They reported that 78% of their patients had a satisfaction score of <3 points using their own symptom scale. Semen analyses done before and after treatment were unchanged. Target temperatures were higher in the prostate and reached 90° to 100°C in the central portion of the lesion created by the radiofrequency.

EXPERIMENTAL THERAPY FOR BACTERIAL PROSTATITIS

Finally, a study has looked at the effects of microwaves and electromagnetic energy on *Escherichia coli* and *Enterobacter cloacae*. They found that microwaves alone have in vitro bactericidal effects independent of heat.[14] Electromagnetic waves were disappointing in their bactericidal effects. Liatsikos *et al.*[15] looked at a Nitinol coil (Shape Memory Applications, Inc., Johnson Matthey, Inc., West Chester, PA) attached to an electrical generator and found that the heat generated was responsible for the bactericidal effects.[15] Their goal was to use a stent in conjunction with an electrical generator to treat bacterial prostatitis.

CONCLUSIONS

Only 2 phase 3 clinical trials using heat therapy for CP have been performed. A study by Shah *et al.*[4] was presented at the American Urological Association (AUA) in 1993 and subjectively compared 2 groups, one receiving transrectal microwave therapy and the other group receiving a sham treatment. The other study by Nickel and Sorenson[9] looked at 20 patients using TUMT. Thus, in a review of heat therapy for the treatment of NBP only 2 studies were controlled, and only Nickel and Sorenson[9] used a validated instrument for its outcome. Any trial with heat therapy must use a validated symptom index. It must be sufficiently powered to make a formal statement on the treatment, and the follow-up period should be for $\geq$12 to 24 months. Until there are more data to support the use of these heat therapies in the treatment of prostatitis, their use in patients should be considered a last resort.

REFERENCES

1. Servadio C, Leib Z, and Lev A: Diseases of prostate treated by local microwave hyperthermia. Urology **30:** 97–99, 1987.

2. Rigatti P, Buonaguidi A, Grasso M, *et al:* Morphodynamic and biochemical assessment of seminal plasma in patients who underwent local prostatic hyperthermia. Prostate **16:** 325–330, 1990.

3. Servadio C, and Leib Z: Chronic abacterial prostatitis and hyperthermia. A possible new treatment? Br J Urol **67:** 308–311, 1991.

4. Shah TK, Watson GM, and Barnes DG: Microwave hyperthermia in the treatment of chronic abacterial prostatitis and prostatodynia: results of a double blind placebo controlled trial [abstract]. J Urol **149:** 405A, 1993.

5. Montorsi F, Guazzoni G, Bergamaschi F, *et al:* Is there a role for transrectal microwave hyperthermia of the prostate in the treatment of abacterial prostatitis and prostatodynia? Prostate **22:** 139–146, 1993.

6. Baert L, Willemen P, Ameye F, *et al:* Transurethral microwave hyperthermia: an alternative treatment for prostadynia? Prostate **19:** 113–119, 1991.

7. Nickel JC, and Sorenson R: Transurethral microwave thermotherapy of nonbacterial prostatitis and prostatodynia: initial experience. Urology **44:** 458–460, 1994.

8. Choi NG, Soh SH, Yoon TH, *et al:* Clinical experience with transurethral microwave thermotherapy for chronic nonbacterial prostatitis and prostatodynia. J Endourol **8:** 61–64, 1994.

9. Nickel JC, and Sorensen R: Transurethral microwave thermotherapy for nonbacterial prostatitis: a randomized double-blind sham controlled study using new prostatitis specific assessment questionnaires. J Urol **155:** 1950–1954, 1996.

10. Glass JM, Bdesha AS, and Witherow RO: Microwave thermotherapy: a long-term follow-up of 67 patients from a single centre. Br J Urol **81:** 377–382, 1998.

11. Nickel JC, Siemens DR, and Johnston B: Transurethral radiofrequency hot balloon thermal therapy in chronic nonbacterial prostatitis. Tech Urol **4:** 128–130, 1998.

12. Chiang PH, Tsai EM, and Chiang CP: Pilot study of transurethral needle ablation (TUNA) in treatment of nonbacterial prostatitis. J Endourol **11:** 367–370, 1997.

13. Lee KC, Jung PB, Park HS, *et al:* Transurethral needle ablation for chronic nonbacterial prostatitis. BJU Int **89:** 226–229, 2002.

14. Sahin A, Eiley D, Goldfischer ER, *et al:* The in vitro bactericidal effect of microwave energy on bacteria that cause prostatitis. Urology **52:** 411–415, 1998.

15. Liatsikos EN, Dinlenc CZ, Kapoor R, *et al:* Transurethral microwave thermotherapy for the treatment of prostatitis. J Endourol **14:** 689–692, 2000.