HIGH ENERGY THERMOTHERAPY IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA: RESULTS OF THE EUROPEAN BENIGN PROSTATIC HYPERPLASIA STUDY GROUP


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ABSTRACT

Purpose: We documented the results of high energy transurethral microwave thermotherapy in the treatment of benign prostatic hyperplasia.

Materials and Methods: We evaluated 116 patients following transurethral microwave thermotherapy according to symptom scores, transrectal ultrasound, free voiding and pressure-flow study parameters.

Results: Significant improvement was noted in all objective and subjective parameters. Moreover, cavities in the prostatic urethra were observed in almost 40% of the patients.

Conclusions: High energy transurethral microwave thermotherapy is an effective therapy for benign prostatic hyperplasia. Patients with larger prostates and moderate to severe bladder outlet obstruction seem to be the best candidates for this higher energy thermotherapy protocol, although morbidity is increased.

KEY WORDS: prostatic hypertrophy; hyperthermia, induced; microwaves

Bladder outlet obstruction in men has been a clinical problem throughout medical history. As early as the 17th century it was suggested that benign prostatic hyperplasia (BPH) could result in mechanical obstruction of the bladder outlet, which may eventually cause lower urinary tract symptoms, inefficient bladder emptying with poor urinary flow and/or post-micturition residual urine. At this juncture the patient usually seeks medical advice either because of troublesome symptoms or complaints secondary to the worsened voiding, for example recurrent urinary tract infections.

Presently, transurethral resection of the prostate is the gold standard therapy for BPH, affording excellent results in the hands of the experienced surgeon. The success of transurethral resection of the prostate is defined by the immediate resolution of cavities. Long lasting improvement in symptoms and voiding parameters is achieved within a few days of treatment. However, this operation is not to be taken lightly. Although the mortality rate has decreased to 0.5%,2 the morbidity rate after transurethral resection of the prostate is still 18% and has not altered significantly within the last 15 years. Consequently, despite the proved safety and efficacy of this procedure, its morbidity as well as its relatively high cost and invasive nature have led many investigators to search for an alternative treatment.

Many techniques that minimize the physiological effects associated with prostate surgery are currently being assessed, including use of prostatic stents,3 transurethral needle ablation,4 high intensity focused ultrasound,5 transurethral microwave thermotherapy4 and laser therapy.7 The question as to which technique is appropriate in any individual is answered largely by knowing the outcome of each of these therapies. Despite the encouraging results claimed for all of the new techniques, transurethral resection of the prostate continues to surpass its competitors. However, the results of high energy thermotherapy seem to shed a new light on this discussion.

The results reported with lower energy thermotherapy using Prostasoft 2.08 in the treatment of BPH are promising. Overall symptomatic improvement has been reported in the majority of patients in conjunction with improvement of voiding parameters.9-10 The Madsen symptom score decreased from a mean of 13 before treatment to about 4 after treatment, while mean maximum flow change ranged from 2 to 3 ml. per second. It has been suggested that the placebo response with this modality may contribute considerably to treatment outcome. However, 5 sham controlled studies have demonstrated that the effect of transurethral microwave thermotherapy is greater than can be accounted for by either the associated urethral instrumentation or by any placebo effect.11 The re-treatment rate after transurethral microwave thermotherapy was reportedly 0.5 to 11% at 1 year of followup.9,10,12 An increase in thermal dose can be seen with the evolution of thermal treatment modalities. The elevation of intraprostatic temperatures as measured by invasive thermometry during transurethral microwave thermotherapy using version 2.0 operating software has been shown to be broadly correlated with clinical outcome.13 Program version 2.0 was modified to provide more power at a maximum of 70 watts, and uses a higher rectal threshold leading to an increase in the energy delivered to the prostate. This new version of the operating software, known as Prostasoft version 2.5, is currently under evaluation. In contrast to earlier reports on results achieved with lower energy thermotherapy, the results with these higher energy levels seem to be excellent, and in a subgroup of patients they are even comparable to those of surgical therapy. We present the results of a multicenter study using high energy thermotherapy for the treatment of BPH.

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PATIENTS AND METHODS

Patients recruited for the study had a Madsen symptom score of 8 or more, maximum flow rate 15 ml per second or less, post-void residual 350 ml or less and voided volume 100 ml or more. Assessment of these patients included history with symptom scores, physical examination with digital rectal examination, biochemistry investigations including prostate specific antigen, urinalysis, urine culture, transrectal ultrasonography of the prostate, uroflowmetry, post-void residual measurement and a urodynamic investigation including pressure-flow studies. The results of high energy thermotherapy in 116 men with lower urinary tract symptoms and BPH were evaluated, and outcome was correlated with prostate size, International Prostatic Symptom Score (I-PSS), Madsen symptom score, free flow voiding parameters and grade of bladder outlet obstruction. Followup was performed at 4, 12, 26 and 52 weeks after treatment.

We used the Prostatron\textsuperscript{\textregistered} device with a C00 treatment catheter consisting of a microwave dipole antenna positioned 10 mm. below the Foley balloon and mounted in a water-cooled transurethral probe. Version 2.5 of the high energy operating software provides power at a maximum of 70 watts to followup. Mean Madsen symptom score at baseline was 13.6, and improved to 9.4 at 4 weeks, 6.0 at 12 weeks, 5.5 at 26 weeks and 4.9 at 52 weeks of followup (fig. 1, A). The I-PSS showed a similar pattern, with improvement from a mean of 17.5 at baseline to 13.9 at 4 weeks, 8.2 at 12 weeks, 7.9 at 26 weeks and 7.1 at 52 weeks of followup (fig. 1, B). Maximum flow rate improved from 9.6 ml per second at baseline to 9.8 at 4 weeks, 15.2 at 12 weeks and 14.1 at 26 weeks of followup. These improvements were sustained to 52 weeks, with a maximum flow rate of 14.5 ml per second (fig. 1, C). The voided volume during followup increased slightly (fig. 2, A), while the post-void residual decreased significantly from 73 ml at baseline to 40 ml at 4 weeks, 27 at 12 weeks, 33 at 26 weeks and 25 at 52 weeks of followup (fig. 2, B). Mean duration of transurethral drainage was 14.3 ± 15.2 days (range 0 to 105).

Transrectal ultrasonography at 3 months of followup identified a cavity in 97% of the patients (fig. 3). There appeared to be good statistical correlation between the presence of cavi ties and uroflowmetry improvement (p = 0.003). Maximum flow rate improved from 9.7 ml per second at baseline to 17.9 ml per second in patients with a cavity on transrectal ultrasonography and from 9.6 to 13.6 ml per second in those without a cavity. Currently, data for 83 patients are available for urodynamic analysis. At 6 months after transurethral microwave thermotherapy a statistically significant improvement was noted for all pressure-flow parameters, which is also clearly illustrated in the Abrams-Griffith nomogram (fig. 4 and table 1). Baseline parameter stratification versus treatment outcome showed that particularly patients with larger prostates and moderate to severe bladder outlet obstruction respond best to high energy transurethral microwave thermotherapy (table 2). These patients showed a significant improvement in objective and subjective parameters. The relationship between maximum flow rate at baseline and treatment outcome was much less. There appeared to be no relationship between treatment outcome and Madsen symptom score at baseline.

High energy thermotherapy resulted in considerable morbidity. Irritative voiding complaints were noted in a large number of patients for up to 2 to 4 weeks, and transient hematuria was present in most patients during the first days after treatment. Finally, retrograde ejaculation was documented in a third of the patients who had antegrade ejaculation before treatment.
Since men with BPH are often of advanced age with cardiac disease a combination that can be characterized by multiple co-morbidities, the assessment of the response to treatment is traditionally based on the objective results obtained by means of dynamic ultrasound and the observed improvement in urinary tract symptoms. In practice, however, these results are not always sufficient to fully evaluate the patient's condition and the treatment's effectiveness. In addition, the use of active surveillance in patients with moderate symptoms and low-risk disease is becoming more common. This approach allows for a more personalized management, taking into account the patient's specific characteristics and preferences.

**Discussion**

**Fig. 4**. Absolute change in serum prostate specific antigen (PSA) levels over time in patients with or without previous transurethral resection of the prostate.

**Fig. 5**. Comparison of the objective and subjective outcomes of the treatment in patients with or without previous transurethral resection of the prostate.

**Fig. 6**. Comparison of the changes in International Prostate Symptom Score (IPSS) and Quality of Life (QoL) between the two groups.

**Fig. 7**. Comparison of the changes in post-void residual urine volume between the two groups.

**Fig. 8**. Comparison of the changes in prostate-specific antigen (PSA) levels before and after the treatment.
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The changes in pressure-flow study parameters were only moderate with the lower energy Prostasoft 2.0 software. We concluded that only a certain type of obstruction responded favorably to thermotherapy. In general, however, severe obstruction is not cured following low energy thermotherapy. Analysis of the urodynamic data at 6 months after transurethral microwave thermotherapy using Prostasoft 2.5 showed that 80% of obstruction patients appeared to be cured (fig. 4). A significant decrease in all obstruction parameters was noted overall (table 1). One can conclude that transurethral microwave thermotherapy using Prostasoft version 2.5 is able to relieve bladder outlet obstruction.

From an earlier study we learned that no single clinical parameter could predict which patients would respond best to low energy thermotherapy. Using high energy thermotherapy it appears that patients with severe obstruction and larger prostates will respond best. Further studies are required to explain this phenomenon. A possible explanation for the favorable outcome of treatment of larger prostates is a difference in tissue composition and tissue perfusion. It is well known that stromal tissue responds differently to heat than glandular tissue. Larger prostates may have a different distribution of stromal and glandular tissue, and consequently they may respond differently to thermotherapy. We also know that the temperature increase in the prostate depends strongly on the tissue perfusion, and that perfusion is known to increase with temperature during thermotherapy. One can speculate that in larger prostates the tissue perfusion is less efficient than in smaller prostates, and that perhaps as a consequence higher temperatures can be achieved resulting in necrosis with formation of a cavity. Current thermotherapy systems do not consider the effect of tissue perfusion on the efficacy of the treatment.

Although urine flow is improved, the morbidity caused by high energy transurethral microwave thermotherapy is increased compared to lower energy protocols. The high energy treatment is well tolerated by the patients but pain medication must be administered before or during therapy in most cases. On a trial and error basis, 30 mg. morphine sulfate administered 2 hours before therapy resulted in an almost complaint-free treatment. If requested, patients also were given either 10 mg. diazepam and/or 0.10 mg. fentanyl during treatment. Perception of discomfort during transurethral microwave thermotherapy may vary from a mild sensation of perineal warmth and a mild urge to urinate to significant discomfort. However, the morbidity is clearly lower with transurethral microwave thermotherapy than with transurethral resection of the prostate. Transurethral microwave thermotherapy can still be performed as an outpatient procedure without general anesthesia, and it is particularly well suited for patients in poor health. Occasionally, hematuria and tissue slough are noted, and urinary retention is ex-

**Table 1. Urodynamic data at baseline and after treatment**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure at maximum flow</td>
<td>64 ± 23</td>
<td>29 ± 16</td>
</tr>
<tr>
<td>Linear passive urethral resistance</td>
<td>2.9 ± 1.3</td>
<td>1.3 ± 1.1</td>
</tr>
<tr>
<td>Urethral resistance factor</td>
<td>41 ± 15</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>Minimal urethral opening pressure</td>
<td>33 ± 17</td>
<td>16 ± 9</td>
</tr>
<tr>
<td>Theoretical urethral lumen</td>
<td>2.8 ± 1.3</td>
<td>6.2 ± 5.1</td>
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**Table 2. Outcome of subjective (Madsen symptom score) and objective (maximum flow and pressure at maximum flow) parameters according to results of maximum flow at baseline, prostate volume and grade of obstruction**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. Pts.</th>
<th>Mean Madsen Symptom Score ± SD</th>
<th>Mean Maximum Free Flow ± SD</th>
<th>Mean Detrusor Pressure at Maximum Flow ± SD</th>
</tr>
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<tbody>
<tr>
<td>Maximum free flow (ml/sec):</td>
<td></td>
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<tr>
<td>12 or More</td>
<td>36</td>
<td>13.8 ± 3.7</td>
<td>5.0 ± 4.9</td>
<td>67 ± 21</td>
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<tr>
<td>Less than 12</td>
<td>80</td>
<td>13.6 ± 3.6</td>
<td>6.5 ± 4.4</td>
<td>62 ± 24</td>
</tr>
<tr>
<td>Prostatic vol. (cc):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 or More</td>
<td>77</td>
<td>15.4 ± 3.6</td>
<td>6.8 ± 4.3</td>
<td>68 ± 21</td>
</tr>
<tr>
<td>Less than 40</td>
<td>39</td>
<td>14.3 ± 3.7</td>
<td>6.4 ± 5.0</td>
<td>53 ± 24</td>
</tr>
<tr>
<td>Linear passive urethral resistance</td>
<td></td>
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<td>relation</td>
<td></td>
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<tr>
<td>3 or More</td>
<td>52</td>
<td>13.7 ± 3.5</td>
<td>5.7 ± 4.4</td>
<td>78 ± 16</td>
</tr>
<tr>
<td>Less than 3</td>
<td>31</td>
<td>14.2 ± 3.9</td>
<td>6.0 ± 4.6</td>
<td>40 ± 10</td>
</tr>
</tbody>
</table>
Formation of cavities after treatment correlated well with severe bladder outlet obstruction and larger prostates.

No bladder neck contraction or urethral strictures have been noted to date. Treatment was repeated in 3 patients because they were not satisfied with the result. From the long-term followup data using Prostasoft 2.0 we have learned that the re-treatment rate at 1 year is estimated up to 10%, while 3-year followup data by de Wildt and de la Rosette, and Dahlstrand et al indicate that clinical benefit is sustained for this period. One may expect that the results achieved with the higher energy software are at least as good.

In conclusion, high energy transurethral microwave microwaves thermotherapy shows significant subjective and objective improvement. The results are similar to those of patients with severe bladder outlet obstruction and large prostates. Formation of cavities after treatment correlated well with better clinical outcome.

REFERENCES

EDITORIAL COMMENT

The authors introduce the results of a multicenter trial of high energy transurethral microwave thermotherapy. In this regard the lower energy Prostasoft 2.0 software was altered. The power was increased to a maximum of 70 watts compared to 60 watts, and rectal temperature safety thresholds were increased from 42.5 to 43.5C. Of
116 patients treated 67 were followed for 1 year. The overall magnitude of response in terms of symptom scoring, peak flow rate and post-void residual seems to be superior to that obtained with the prior software (references 6, 8 to 10, 12 and 13 in article).

The authors attribute the improved results to a higher energy delivered to the prostate, resulting in a wider zone of tissue destruction and subvesical cavities in 37% of the patients. Thus, improvement in mean peak flow rate changes at 12 months approached 5 cc per second with a statistically significant decrease in post-void residual and an increase in voided volume. However, symptomatic improvement does not appear to be significantly different than what can be achieved in symptom score with the Prostasoft 2.0 software. The downside to using this software, however, has been an increase in the morbidity of the procedure and prolonged retention rate. These morbidities remain substantially less than those of transurethral resection, since patients are treated on an outpatient basis without requiring general anesthesia, although liberal parenteral sedation and analgesia were necessary. Considerable irritative voiding complaints that persisted for up to 4 weeks after the procedure are reminiscent of the experience with laser prostatectomy.

It is clear that transurethral microwave thermotherapy is developing its role as an alternative in the management of BPH. The investigators continue to provide these data. A randomized prospective study with this large population of patients comparing Prostasoft versions 2.0 and 2.5 more clearly have placed the high energy treatment in its proper perspective. While it is apparent that symptomatic improvement is substantially the same for both versions, is it necessary to increase morbidity to improve urodynamic parameters? Does the creation of a subvesical cavity result in a more durable treatment? These questions will be answered as transurethral microwave thermotherapy continues to increase its role in the overall management of this disease.

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