RESPONDERS AND NONRESPONDERS TO TRANSURETHRAL MICROWAVE THERMOTHERAPY: A MULTICENTER RETROSPECTIVE ANALYSIS

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ABSTRACT

Purpose: We attempted to identify any parameter that could possibly lead to a successful treatment outcome after transurethral microwave thermotherapy.

Materials and Methods: Clinical parameters and treatment profiles of 292 patients were analyzed in a retrospective multicenter manner. Responder and nonresponder groups were identified according to a given definition.

Results: No statistically significant differences in baseline characteristics were found. Responders showed a 76% symptomatic improvement rate compared to 27% in nonresponders, and an 82% improvement rate in peak flow compared to a 5% decrease in nonresponders. Responders also showed a significantly greater increase in posttreatment PSA level and a significantly greater amount of energy released during treatment.

Conclusions: No baseline clinical parameter is capable of predicting treatment outcome.

Keywords: prostatic hypertrophy; microwaves; hyperthermia, induced

Microwave heating of the prostate is a fascinating approach to the treatment of voiding disturbances in patients with benign prostatic hyperplasia (BPH). There are 2 basic concepts: hyperthermia in which the prostate temperature is not allowed to exceed 45°C, and thermotherapy in which the target temperature is greater than 45°C. A recent multicenter study showed that hyperthermia seems likely to be ineffective in the treatment of BPH and, thus, not to be recommended.

Thermotherapy applies high power microwave energy deep within the lateral prostatic lobes. The results of transurethral microwave thermotherapy are promising. It is presumed that clinical benefit is achieved by a small decrease in adenoma volume and the destruction of certain specific cell types that have some role in the development of bladder outlet obstruction. The clinical improvement has been shown not to be due to a placebo effect or the result of the associated urethral instrumentation in randomized trials of transurethral microwave thermotherapy versus a sham procedure. However, the criteria currently used for inclusion do not prevent a high variability in terms of clinical response to transurethral microwave thermotherapy and treatment outcome.

Clinical experience has shown that significant improvement of subjective and objective parameters of disease severity is achieved in a subgroup of treated patients. Patient parameters at entry and treatment parameters have been investigated in different series for possible correlation with treatment outcome. For patient selection, the specific type and grade of obstruction at screening were correlated significantly with the response rate in a multicenter European study. Analysis of different treatment parameters that are currently monitored during microwave treatment to date has failed to identify any difference between treatments leading to successful outcome and those producing no change for the individual patient. More recently, analysis of patients undergoing invasive thermometry of the prostate during treatment suggested a significant correlation between the amount of heat induced within the gland and flow rate improvement. We investigate further patient treatment profiles to identify any parameter that could possibly lead to a successful treatment outcome. Digital records of the microwave treatments from a large series of patients undergoing microwave therapy at 17 different prostate centers worldwide constitute the material for the study.

PATIENTS AND METHODS

Data from BPH patients undergoing microwave thermotherapy at 17 different centers were collected. The same instrument and treatment software were used at the various centers, and treatments were performed according to a common study protocol. Treatment was given on an ambulatory basis and the method has been described in detail previously. A representation of a treatment session, the position of the catheter and rectal probe, and a treatment profile are demonstrated in figure 1. During transurethral microwave thermotherapy the microwave energy is emitted to the prostate resulting in heat. To prevent damage to urethral mucosa or the rectal wall, 1 thermal sensor is positioned in the treatment device and 3 sensors are placed in the rectal probe to monitor the urethral and rectal wall temperatures. When the maximum allowed temperature is detected by 1 of these sensors an alarm automatically interrupts the treatment. Therapy is resumed when the temperature decreases to a certain level.
Screening consisted of a patient history with the Madsen-
Iversen symptom score, physical examination with digital
rectal examination of the prostate, hematology and blood
chemistry studies, including prostate specific antigen (PSA)
measurements, electrocardiography, chest x-ray, kidney and
bladder ultrasound imaging or excretory urography, trans-
rectal ultrasound of the prostate and uroflowmetry (twice)
with measurements of post-void residual volume using ultra-
sound. All patients studied were candidates for transurethral
resection of the prostate and had a Madsen-Iversen symptom
score of 8 or more, maximum flow rate 15 ml per second or
less and post-void residual volume 250 ml or less. Patients
were excluded from the trial because of an obstructive pro-
static middle lobe, complications of BPH, suspicion of prostate
cancer, presence of any condition that could interfere with
bladder dynamics and patient compliance to the protocol.

Each center was asked to provide case record forms and
copies of the treatment computer files of at least 10 respond-
ers and 10 nonresponders to microwave thermotherapy. Re-
sponders were identified by a Madsen-Iversen symptom score
of 3 or less, or 50% or greater decrease at month 6, a maxi-
mum flow rate of 15 ml per second or more, or 50% or greater
improvement and a post-void residual volume of 50 ml or
less or 50% or greater improvement at 6 months. Nonre-
spenders were identified by a Madsen-Iversen symptom score
of 8 or more or 80% or less improvement, a maximum flow
rate of 10 ml per second or less, or 20% or less improvement,
and a post-void residual volume of 200 ml or more, or 50% or
less decrease at 6 months. At each center data were derived
from consecutive series of patients satisfying the described
criteria.

Followup visits, including symptom evaluation by Madsen-
Iversen symptom score, flow rate measurements by free flow
uroflowmetry and residual urine measurement by ultrasonic,
were scheduled at 1, 3 and 6 months after treatment. Blood
samples were collected at selected sites at 1 day, and 1
and 12 weeks after thermotherapy. Quality data control
included survey of the received case record forms and
treatment files. Only patients with complete data bases
were considered evaluable for analysis. Data collected from
case record forms and retrieved from treatment files were
entered in a computer file and analyzed by a statistical
program.

RESULTS

Of 292 patients evaluable for analysis 136 were responders
and 156 were nonresponders. Analysis of patient parameters
at screening showed no significant difference between the 2
groups (table 1). Changes in Madsen-Iversen symptom score,
maximum flow rate and post-void residual volume are pre-
sented in figure 2. Responders showed an average improve-
ment of 76% for Madsen-Iversen symptom score and an in-
crease in maximum flow rate of 82%, with a decrease of 37%
in post-void residual volume (table 2). Nonresponders had an
average decrease of 27% for symptom score, an actual de-
fine in flow rate of 5% and only a decrease of 14% in
post-void residual volume.

Screening plasma levels of PSA were comparable between
the 2 groups. Heat produced by microwave thermotherapy in
the prostate gland is responsible for the observed increase in
PSA level. Interestingly, at week 1 significantly higher val-
ues were measured in responders (+371%) compared to non-
responders (+176%). PSA values at 3 months were again
comparable between the 2 groups and did not differ signifi-
cantly from baseline (fig. 3).

Different parameters derived from digital records of the
microwave treatments were analyzed (fig. 4). The amount of
energy released during treatment, measured as total energy
dose, average dose and maximum power output, was signif-
icantly different in the 2 groups. The higher amount of en-
ergy released in the responder group resulted in a higher
temperature at the level of the urethra. The number of ure-
thral alarms was greater in responders versus nonre-
spenders but the difference was not significant (fig. 5). Not-
withstanding a higher energy release in responders,
temperatures recorded at the level of the rectal wall were
comparable in the 2 groups. Nevertheless, fewer rectal
alarms were observed in responders compared to nonre-
spenders.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td></td>
<td>Responders</td>
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<tr>
<td>Age (yrs.)</td>
<td>66.8 ± 7.0</td>
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<tr>
<td>Prostate vol. (ml.)</td>
<td>45.0 ± 18.0</td>
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<tr>
<td>Madsen score</td>
<td>13.7 ± 4.0</td>
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<tr>
<td>Maximum flow rate (ml/sec.)</td>
<td>8.8 ± 3.7</td>
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<tr>
<td>Post-void residual vol. (ml.)</td>
<td>960 ± 158.0</td>
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<tr>
<td>PSA (ng/ml.)</td>
<td>4.1 ± 4.3</td>
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**Table 2. Values at baseline and at 6 months**

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
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<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
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<tr>
<td>Madsen score (ml/sec)</td>
<td>13.7 ± 4.0</td>
<td>13.9 ± 4.2</td>
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<tr>
<td>Maximum flow rate (ml/sec)</td>
<td>8.8 ± 3.7</td>
<td>8.3 ± 3.3</td>
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<tr>
<td>Post-void (ml)</td>
<td>96.0 ± 15.0</td>
<td>78.0 ± 80.0</td>
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<tr>
<td><strong>6 Mos.</strong></td>
<td></td>
<td></td>
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<tr>
<td>Madsen score (ml/sec)</td>
<td>3.2 ± 3.3</td>
<td>9.6 ± 4.0</td>
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<tr>
<td>Maximum flow rate (ml/sec)</td>
<td>16.0 ± 6.7</td>
<td>7.9 ± 3.0</td>
</tr>
<tr>
<td>Post-void (ml)</td>
<td>35.0 ± 50.0</td>
<td>67.0 ± 77.0</td>
</tr>
</tbody>
</table>

**Fig. 2. Difference in symptom score, post-void residual volume, (PVR) and maximum flow rate (Qmax) between responders and nonresponders at baseline (Pre), and 3, 6 and 12 months after treatment.**

**Fig. 3. Changes in PSA level (ng./ml.) between responders and nonresponders at baseline, and 1 day, 7 days and 3 months after treatment.**

**Fig. 4. Difference in maximum (Max) power, average power and total administered amount of energy between responders and nonresponders.**

**Fig. 5. Difference in number of rectal and urethral alarms between responders and nonresponders.**

The outcome of thermotherapy has been shown previously to be variable between different sites.\(^3\),\(^4\),\(^5\),\(^6\),\(^7\),\(^8\),\(^12\) To identify selection criteria that could possibly predict successful treatment outcome, a large series of patients was evaluated according to the response to treatment. Responder and nonresponder characteristics at screening were not statistically different, which further supports a previous supposition from our group that currently only baseline urodynamic parameters can predict clinical outcome from microwave treatment.\(^9\) Provided the 2 groups of patients were comparable at baseline, a different microwave treatment profile could have been responsible for the different outcome in the 2 populations. The treatment profile reflects the energy delivered to the prostate, and depends on the number of the rectal and urethral alarms (fig. 1). The alarms result in a safe treatment but they may limit the emission of microwave energy. In view of the results achieved with higher energy levels, we believe that the safety of treatment obviously interferes with efficacy. One cannot have high temperatures within the prostate using low power levels.\(^10\) We know that the amount of heat produced within the prostate is correlated with objective clinical outcome but such parameters are not available in this series. Nevertheless, we still have an indirect measure of intraprostatic temperatures, which is given by the elevation of PSA on the days following transurethral microwave thermotherapy. We do not know whether epithelial cell damage is
TRANSURETHRAL MICROWAVE THERMOTHERAPY

of any importance in the clinical response to microwave therapy but it is certainly 1 of the 3 major cellular components of BPH. Interestingly, the variation of the PSA level within 1 week after treatment was significantly different in the 2 groups. Variation among the individual patients is high and reflects the different response of the individual prostate to microwave treatment, which we observed in previous studies. The kinetics of the PSA increase are outside the objectives of our study but they certainly deserve attention in the future. The concept was confirmed in a recently conducted placebo controlled study.3

The key questions are why some patients achieve a higher intraprostatic temperature than others and whether this is dependent on differing tissue architecture and blood supply in some prostates. Answering such questions will significantly influence patient selection and the design of new treatment software in the future.

Analysis of different treatment parameters has shown that the amount of energy released during treatment differs significantly in the 2 groups and more energy was delivered in responders compared to nonresponders. The observation was confirmed by the evaluation of 3 separate parameters: maximum power output during treatment, and total and average energy doses. Interestingly, the energy applied cannot be related to prostate size.

What happened to this greater amount of energy released into the prostate of patients who did well? A higher energy dose produced a higher urethral temperature, which is not evident when examining the peak urethral temperature achieved during treatment but it was clear if we note the maximum urethral temperature sustained for at least 3 minutes. A higher urethral temperature has, of course, triggered a greater number of urethral alarms, although the difference between the 2 groups was not significant because of the high variability of this parameter in different treatments (0 to 150). Transient interruption of microwave emission seems not to be detrimental to treatment outcome or the total energy dose. Therefore, where is all this energy going? The flux of energy emitted by the microwave antenna passes through the prostate from the urethra to the rectum. As the irradiative energy is absorbed by tissue it is transformed into heat energy and the temperature increases. When temperatures increase vasodilatation occurs creating a heat sink, which may carry away significant amounts of heat. If irradiative energy is largely absorbed by prostatic tissues then rectal temperature cannot increase (by lack of energy) and, consequently, we expect fewer rectal alarms. Interestingly, this is what happened in the responder group. Lower temperatures were measured in the rectal wall of these patients and fewer alarms were recorded.

A higher energy dose with lower rectal temperature may be dependent on 2 different phenomena: either a higher energy absorption by the prostate tissue with a high intraprostatic temperature or a higher energy dissipation from a major blood supply with little temperature increase within the gland. Because patients with a higher energy deposition and lower rectal temperatures have a more successful treatment outcome, better energy deposition is more likely to be responsible for fewer rectal alarms observed in responders.

CONCLUSIONS

None of the baseline parameters used within our study was able to define the ideal patient for and predict the result of treatment. Changes in PSA levels and energy absorption of the prostate merely reflect the heterogeneity of the disease and variability of outcome to this treatment modality. Tissue architecture of the prostate gland and its relative blood supply might have a role in determining the outcome of microwave heating.12 Investigation of possible correlations among these parameters might be important to understand the mechanism of therapeutic effect of microwave heating on BPH, resulting in more efficient heat induction of the prostate.

Vincent Cabane assisted with the study.

REFERENCES