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A 12-month study of the placebo effect in transurethral microwave thermotherapy

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Objective To determine the placebo effect of transurethral microwave thermotherapy (TUMT) in the treatment of benign prostatic enlargement (BPE).

Patients and methods A prospective, randomized sham-controlled study in 93 patients (mean age 65, range 50–88) was conducted at two centres comparing TUMT or a sham treatment. Patients randomized to receive sham treatment underwent the same initial procedure as for TUMT, but the complete procedure was simulated on the visual display with no application of microwave energy. If the patient's condition had not improved after 3 months, a second genuine TUMT treatment was given at the patient's request.

Results After 3 months there were significant clinical and statistical differences in efficacy between the

groups; 62% and 18% of patients had a >50% improvement in symptom score in the treated and sham groups, respectively ($P=0.001$). The corresponding changes in flow rate were 36% and 11% ($P=0.002$), respectively. After 1 year, 63 patients were divided into those that had TUMT initially, those that had sham initially but subsequently had TUMT and those whose sham procedure had led to sufficient clinical improvement to require no further treatment. The two treated groups had a significant improvement over the sham group.

Conclusion The benefit from TUMT cannot be due to a placebo effect alone.

Keywords Benign prostatic enlargement, placebo, thermotherapy (TUMT)

Introduction

Several minimally invasive treatments for patients with symptomatic benign prostatic enlargement (BPE) have been introduced recently. Some rely on mechanical disruption or distraction of the prostatic urethra, e.g. balloon dilatation or stenting [1–3] but prostatic heating appears to be the most promising alternative. Heat can be delivered selectively to the prostate using different sources, e.g. high intensity focused ultrasound (HIFU), radiofrequency (transurethral needle ablation, TUNA), endoscopic lasers and microwave devices [4–8]. So far, the microwave techniques have been the most extensively investigated. There are two basic concepts; one is hyperthermia, where the prostatic temperature is not allowed to exceed 45°C and the other is thermotherapy, where the target temperature is >45°C [9–12]. Initially, research was concentrated on the use of hyperthermia delivered with either a transurethral or transrectal applicator. Hyperthermia was evaluated against sham treatment in a multicentre study in which five machines (three transrectal and two transurethral) were tested [13] and which concluded that transrectal hyperthermia

was probably ineffective in the treatment of BPE and thus should not to be recommended [14].

Recently, many researchers have used a higher temperature in microwave treatments, or thermotherapy. These treatments deliver high-power microwave energy deep within the lateral prostatic lobes, causing irreversible cell damage to prostatic tissue but without damaging the urethra. Results of transurethral microwave thermotherapy (TUMT) are very promising, although the degree and significance of the placebo effect remains controversial [15]. Reports from two other groups have suggested that the response to TUMT is significantly greater than that due to any effect of placebo or instrumentation [16,17]. A recent report by Nawrocki *et al.* cast doubt on the validity of these conclusions [18].

In this paper we present the long-term results of a randomized placebo-controlled study conducted in two centres. Moreover, we give an overview of the published placebo-controlled studies on TUMT and discuss the extent of the placebo effect in TUMT treatment of symptomatic bladder outlet obstruction due to BPE.

Patients and methods

From June 1991 to December 1992, 93 men (mean age 65 years, range 50–88) were recruited into the study.

For entry into the study, all patients had to be >45 years old and complaining of symptoms of bladder outlet obstruction for >3 months, have a Madsen symptom score of >8 and urinary free-flow rate estimates of <15 mL/s during two voids of >150 mL. The presence of BPE was confirmed by transrectal ultrasonography (TRUS), the measurement of prostate-specific antigen and, where necessary, by prostatic biopsy. Exclusion criteria were: prostate cancer, prostatitis, urethral stricture, intravesical pathology (stones, neoplasm), neurogenic bladder dysfunction, urinary tract infection, isolated enlargement of the middle lobe, a residual urine volume of ≥ 300 mL, use of drugs influencing bladder or prostate function, previous transurethral resection of the prostate (TURP) or transurethral incision, a metallic pelvic implant, disorders of blood flow or coagulation, diabetes mellitus and mental incapacity or inability to give informed consent.

The assessment before treatment consisted of a general history and complete physical examination. Serum creatinine, urea, and electrolytes and a full blood count were measured, and urine was sent for microbiological and cytological analysis. The severity of symptoms was expressed by a Madsen symptom score [19]. Flow rates were corrected for artefacts by two independent observers (M. H. and M.de W) using the 2-s method [20], with no knowledge of the patient's treatment. The voided volume was correlated with the post-void residual volume (PVR) to give a 'voiding fraction', using the formula: voiding fraction = voided volume / (voided volume + PVR) [21]. TRUS was performed to measure the dimensions and configuration of the prostate and prostatic volume calculated using the formula of Stamey and Terris [22].

The procedures for TUMT treatment have been described previously [8]. When a patient was randomized to receive the placebo (sham) treatment, the whole procedure was simulated but without applying microwave energy. During both active and sham procedures, a real-time treatment profile was displayed on the computer screen and explained to the patient. The sequence of temperature calibration and checks were identical in both groups. At the end of the session, patients were asked to remain in the department until satisfactory voiding had been established. In case of retention, a urethral catheter was placed for 1 week. The baseline tests were repeated at 1, 12 and 52 weeks after treatment. As far as possible, the patient and the investigator were kept unaware as to the treatment administered. When a patient noticed no improvement after 3 months, whether he had previously received a sham or active treatment, a second genuine TUMT was performed on request.

Statistical analysis within each group was carried out using Student's *t*-test (with significance defined as

$P < 0.05$) while the Wilcoxon signed-rank test and the Kruskal-Wallis test were used for comparisons between groups. The chi-squared test was used to assess the significance of differences in response rate between the groups.

Results

There were no statistical differences between either the sham or TUMT group (Table 1). Patients from the London centre were significantly older, had more symptoms, particularly obstructive ones, and a greater residual urine volume than those at Nijmegen (Table 1). There were marginal differences between the entry study groups and those that had a re-treatment TUMT after sham treatment. Eighty-eight patients were available for assessment at 3 months and 63 at 1 year. The fate of the other patients is given in Table 2. The period of follow-up for each group is given as the time after the last treatment session, whether a first or second TUMT or sham, rather than from the beginning of the study.

The 46 patients who received sham treatment experienced a significant improvement in symptoms at 3 months, with the initial mean Madsen score of 12.9 ± 3.1 decreasing to 10.4 ± 4.7 . However, there was no significant change in the peak flow rate (Table 3). Thirteen patients were sufficiently content with their symptoms that no further intervention was required by 1 year, representing the best possible outcome of the sham treatment or the maximum placebo effect. Only the symptom score had improved significantly from baseline. The main complication was the rate of retention. After the genuine TUMT treatment, 10 patients (21%) needed a transurethral catheter, whereas in the sham group, only one patient was unable to pass urine freely.

Following either TUMT or TUMT after a sham treatment, there was a statistically significant improvement in both Madsen score and flow rate over baseline, at both 3 months and 1 year. Comparison with the sham group at 3 months showed a significant difference in outcome for each of the variables. At 1 year, the patients treated by TUMT continued to have a statistically significant improvement over the remaining patients from the sham group in both Madsen score and flow rate. There were no significant differences at 1 year for PVR or voiding fraction amongst the three groups.

Stratification of the three groups by the outcome at 3 months, defined by the criteria for success suggested in the Food and Drug Administration (FDA) guidelines is shown in Table 4. There were more successful patients among those receiving TUMT than among those receiving a sham treatment when assessed by both the Madsen score and peak flow rate, but the difference was not as striking using the change in PVR as a criterion of success.

Table 1 Differences in baseline variables between the contributing centres and in each treatment group

	Age (years)	Prostate volume, (mL)	Madsen score	Peak-flow (mL/s)	PVR* (mL)	Voided fraction(%)
<i>Centre</i>						
Charing Cross						
Mean	67.2	46.3	14.2	9.1	132.5	67.3
SD	8.1	18.1	3.2	2.4	72.8	15.8
Nijmegen						
Mean	63.4	50.8	12.6	9.6	55.2	83.0
SD	6.0	18.2	3.2	2.7	46.8	12.8
<i>P</i> -value	0.016	0.116	0.036	0.269	<0.001	<0.001
<i>Treatment (no. of patients)</i>						
Sham (46)						
Mean	63.9	49.0	12.9	9.6	84.7	77.3
SD	6.0	20.0	3.1	2.7	66.1	15.7
TUMT (47)						
Mean	66.3	48.6	13.7	9.2	93.9	74.9
SD	8.1	16.6	3.4	2.5	75.4	16.6
TUMT after sham (27)						
Mean	65.8	52.0	13.6	9.0	110.0	70.6
SD	6.1	23.9	2.8	3.3	80.4	17.8
<i>P</i> -value	0.197	0.503	0.435	0.385	0.259	0.938

PVR, Post-void residual volume

Table 2 The number of patients in all groups and the treatments and losses during follow-up

Follow-up	Baseline	Numbers of patients (months)		
		3	6	12
Sham	46	43	18	13
Lost to follow-up		2	2	1
Second TUMT			23	4
Other*		1		
TUMT	47	45	36	33
TURP		2	1	1
Lost to follow-up			3	2
Second TUMT			4	
Death†			1	
TUMT after Sham	27	26	23	15
Lost to follow-up			3	6
Laser		1		
Other‡				1
Death†				1
TUMT after TUMT	4	4	4	2
Lost to follow-up				2

* Technical failure. † Not related to treatment. ‡ α1-blocker treatment

Discussion

The placebo phenomenon is difficult to define and the terminology in treatments using devices is still a matter of debate. Traditionally, placebo trials are associated with drug studies and the benefits which a patient may experience while taking a placebo are often assumed to result only from the psychological improvement obtained by contact with those involved in the trial, or by better education in health matters. However, there may also be some improvement due to the natural resolution of the disease process or as a result of the interventions required during the study. Placebo studies do not address fully the problem that the natural history of the disease is necessarily brief, because there are ethical constraints against withholding treatment for a prolonged period. The spontaneous changes occurring in any disease process are best observed by comparing an active treatment to an arm with no treatment, randomly and prospectively. A spontaneous improvement in a patient's condition may seem to occur as the result of the study, e.g. an improved urine flow after more experience or from repeated catheterization studies of BPE. In device-based therapies, the intervention required to prevent the patient knowing which treatment has been received may have a previously unsuspected therapeutic benefit, e.g. the insertion of a urethral applicator during

Table 3 Main follow-up indices in the sham, TUMT and TUMT after sham groups at baseline, 12 and 52 weeks

	Baseline		Follow-up at 12 weeks			Follow-up at 52 weeks		
	Mean	95% CI	Mean	95% CI	P-value	Mean	95% CI	P-value
Madsen symptom score								
Sham	12.9	11.9; 13.9	10.4	8.9; 11.8	0.003	8.2	5.5; 11.0	0.011
TUMT	13.7	12.7; 14.7	4.7	3.6; 5.9	<0.001	4.2	3.0; 5.3	<0.001
TUMT after Sham	13.6	12.4; 14.8	5.4	3.6; 7.2	<0.001	7.0	3.8; 10.2	0.005
Peak flow rate (mL/s)								
Sham	9.6	8.8; 10.4	9.7	8.7; 10.7	0.846	10.5	7.9; 13.1	0.657
TUMT	9.2	8.4; 9.9	13.4	11.7; 15.3	<0.001	13.4	11.6; 15.1	<0.001
TUMT after Sham	9.0	7.6; 10.4	13.4	11.1; 15.7	<0.001	12.8	9.8; 5.8	0.033
Post-void residual urine (mL)								
Sham	84.7	64.0; 105.1	104.1	74.7; 133.4	0.428	56.3	16.9; 95.7	0.433
TUMT	93.9	71.8; 116.0	34.2	19.4; 46.8	<0.001	49.7	33.0; 66.3	0.002
TUMT after Sham	110.0	76.9; 143.2	67.1	37.7; 91.1	0.012	57.3	23.4; 91.1	0.133
Voided fraction (%)								
Sham	77.3	72.4; 82.1	75.4	69.6; 81.3	0.936	83.5	73.8; 93.2	0.814
TUMT	74.9	70.1; 79.8	89.5	85.2; 93.7	<0.001	84.5	79.3; 89.7	<0.001
TUMT after Sham	70.6	63.3; 77.8	81.0	73.8; 88.2	0.015	84.5	77.1; 92.0	0.116

Table 4 The proportional improvement in the main indices at 3 months of follow-up: percentages are based on intention to treat

	Improvement from baseline parameter							
	<25%	≥ 25%	≤ 50%	> 50%	> 75%			
Madsen symptom score								
Sham	26	58%	11	24%	8	18%	4	9%
TUMT	10	21%	8	17%	29	62%	14	30%
TUMT after sham	9	33%	5	19%	13	48%	9	33%
						P=0.002		
						P<0.001		
Peak flow rate (mL/s)								
Sham	31	69%	9	20%	5	11%	4	9%
TUMT	23	49%	7	15%	17	36%	12	26%
TUMT after sham	13	48%	2	7%	12	44%	7	26%
						P<0.002		
						P<0.001		
Post-void residual urine (mL)								
Sham	31	69%	4	9%	10	22%	8	18%
TUMT	18	38%	6	13%	23	49%	21	45%
TUMT after sham	14	52%	6	22%	7	26%	5	19%
						P=0.002		
						P=0.449		

thermotherapy. One of the critical issues for the evaluation of devices for the treatment of symptomatic BPE is whether the placebo response seen with drug studies can be expected with any treatment, be it a device or even surgery.

The results of the present study suggest that there

was indeed a significant placebo/instrumental response in patients undergoing sham treatment. The two other comparisons of TUMT and sham treatment [16,17] also showed similar changes in the Madsen score in both the TUMT and sham arms (Fig. 1a). There are some differences in the peak flow rate changes, in that the study

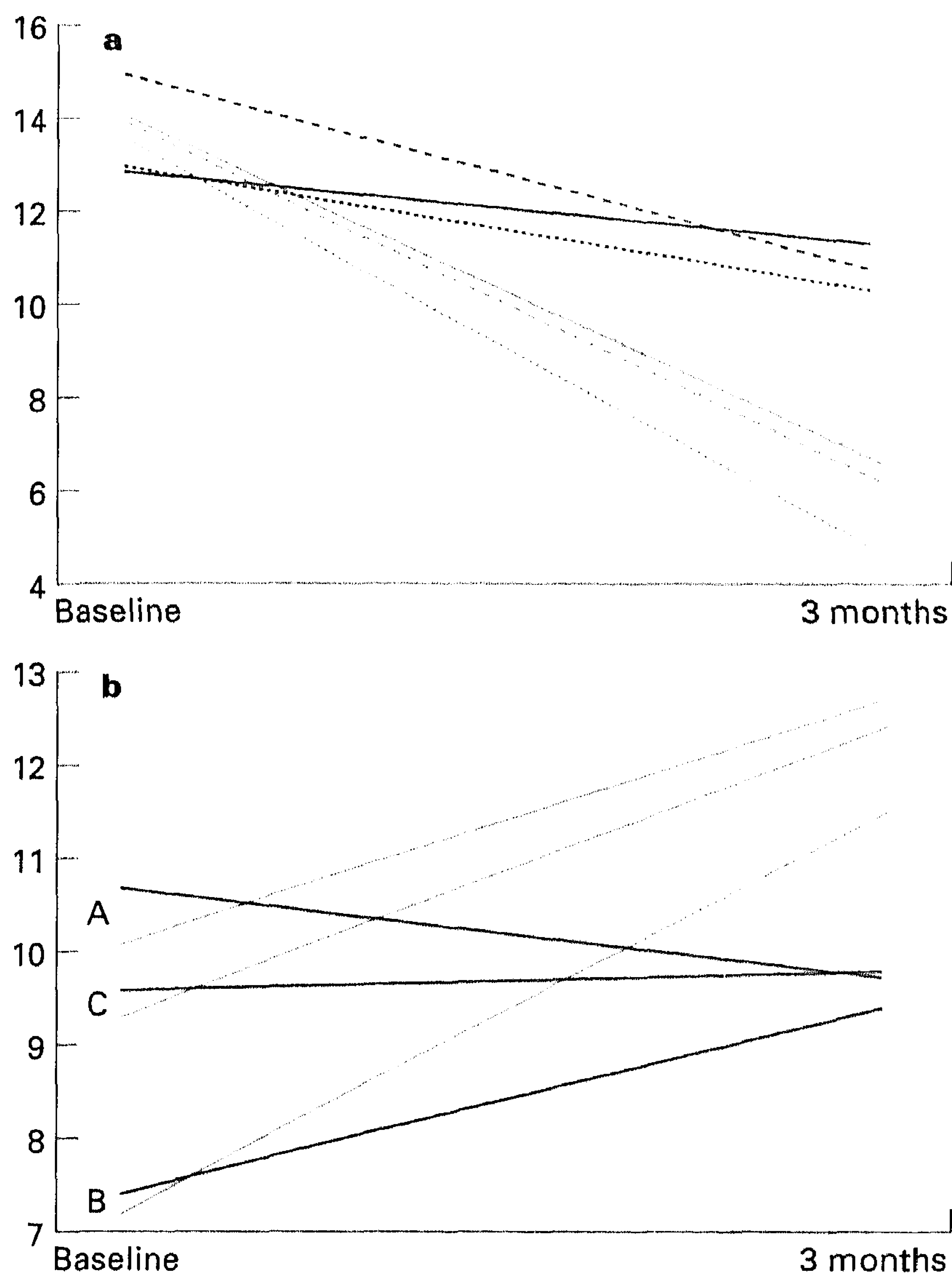


Fig. 1. a, Changes in mean Madsen symptom score. b, Changes in mean peak flow rate (mL/s). Dark green, Sham. Light red, TUMT. A=[13], B=[16], C=Present study.

by Perrin and Devonnee [17] showed a small decline in peak flow at 3 months and the study by Blute *et al.* [16] demonstrated a larger improvement than in the present study (Fig. 1b). The study of Bdesha *et al.* using a transurethral microwave device with no cooling differs from other studies in that they found a 16% improvement in symptoms and a deterioration in peak flow rate and PVR in the sham arm [23]. This result is comparable with the symptomatic improvement of 19% in the current study. One of the best controlled drug studies in patients with symptomatic BPE is that by the International Finasteride study group [24], which had a placebo arm followed for up to 1 year and comprising 154 patients. The mean change in the symptom score was -2.6 , from a baseline of 19.2, using a modified Boyarski score with a maximum of 36. The increase in flow rate was minimal, with an improvement of only 0.4 mL/s from a baseline of 8.6 mL/s in the placebo-treated patients. Jardin *et al.* [25] reviewed the placebo response in studies of alpha-blocking agents and reported a change in flow rate from -2.7 to $+2.3$ mL/s. The placebo response found in TUMT studies is greater than that in many drug studies.

Previous studies comparing TUMT to sham agree that there is a greater benefit from thermotherapy [16,17]. Both the centres participating in the present study reported results at 3 months individually; there was a significant difference between the outcome of sham and TUMT in both [26,27]. However, the study based in London [26] demonstrated little effect of placebo because a few patients in the sham-treated arm deteriorated significantly during the 3-month follow-up, thereby skewing the data. By pooling the data from these two studies, which were carried out according to the same protocol, the evidence for a placebo effect is strengthened. Only one study has concluded that the majority of the effect of TUMT is due to a placebo response [15] but the results lack credibility as they were from a non-randomized, unblinded study. Both the study of thermotherapy by Bdesha *et al.* [17] and the French multicentre study of hyperthermia devices [14] showed no difference in flow rate changes between sham and treatment, but it is presumed that this is due to the small increase in flow rate seen after the application of transurethral microwave energy at lower power and without simultaneous cooling of the applicator [13,23]. The similarity of the improvement in symptom score in a non-irrigated method of thermotherapy, e.g. that used by Bdesha *et al.* [23] with that in the present study is interesting. To date, there is only one paper reporting subsequent treatment of those receiving sham treatment, and a 1-year follow-up which showed similar results to the present study [28]. However, that study comprised few patients and the microwave therapy was more in the range of hyperthermia than in that of thermal therapy. A study of a three-way randomization between sham, TUMT and watchful waiting (WW) comprising 120 patients in total [15] reported that the WW group showed no clinically relevant deterioration or improvement. The sham-treated group had a symptomatic improvement (45%) comparable to TUMT (50%). There was little clinically relevant improvement of the objective variables in the TUMT group and no relevant improvement in the sham-treated group. However, in that study, the patients were selected if they had severe obstruction, as defined by pressure-flow studies, and may not represent a similar population to that in the present study (P. Nawrocki, personal communication). There is evidence to suggest that TUMT has much less effect on patients with more severe obstruction [29].

The conclusion from these comparisons of TUMT and sham treatment must be that there is an effect of heat on bladder outlet function in the older man and that only a small part of the clinical benefit can be accounted for by the effect of placebo or instrumentation. This conclusion is further supported by the analysis of those patients who have transferred from sham to TUMT

treatment. Presumably, these men are not susceptible to a placebo effect and yet the changes after treatment are still very significant, albeit less than occurred in the original treatment group. The difference in outcome between TUMT and TUMT after sham probably results from the exclusion of those responding to the placebo and thus this may be considered to reflect the therapeutic effect of TUMT.

The most cogent argument for a greater benefit from TUMT than from sham treatment is that from the analysis of the rates of response based on the percentage intention-to-treat. The FDA proposed that response should be examined as a percentage change in each individual criteria, as well as in combination; this gives an agreed framework by which to compare the outcome following what are often very different treatments [30]. After sham treatment, only 11% of men had a >50% change in peak flow rate, compared to 36% of men after TUMT. The difference is more striking when comparing the effect on symptom score, with only 18% of patients receiving sham treatment attaining a satisfactory improvement (i.e. >50%) as opposed to 62% of those receiving TUMT.

The present study showed that the difference between sham treatment and TUMT persisted for at least 1 year. Only 10 of the 74 patients who were treated by TUMT required any further intervention within 1 year and of those, only four required TURP, the others being treated by either repeated TUMT or other minimally invasive therapy.

We feel strongly that the evidence for a beneficial effect of heating at 'thermotherapy' temperatures is conclusive and that further randomized sham studies would be unethical. The burden of these types of investigation upon the patient is substantial and should not needlessly be repeated. Now the most important question is how the improvement in voiding is obtained in the absence of any significant loss of prostatic volume. It is clear that the mechanism of action of TUMT is substantially different to the reduction in volume and the formation of a cavity that is obtained with TURP and thus provides an exciting opportunity to provide a genuinely novel treatment for patients with symptomatic BPH. TUMT using this level of heating (Prostasoft version 2.0) is particularly suitable for the treatment of earlier and less severe disease in the younger man who wishes to avoid disturbance to his sexual function or in the elderly with many comorbid conditions precluding a safe resection. It is also important that a proportion of patients respond more to TUMT than do others, possibly because the required threshold temperature of 45°C is not always achieved [31]. Furthermore, sophisticated methods to select patients are required to make better use of the advantages of this minimally invasive therapy.

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