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LONG-TERM POOLED ANALYSIS OF MULTICENTER STUDIES OF COOLED THERMOTHERAPY FOR BENIGN PROSTATIC HYPERPLASIA: RESULTS AT THREE MONTHS THROUGH FOUR YEARS

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ABSTRACT

Objectives. To determine the long-term efficacy of cooled thermotherapy in the treatment of lower urinary tract symptoms of clinical benign prostatic hyperplasia.

Methods. A total of 541 men underwent cooled thermotherapy treatment in six multicenter studies in the United States, England, and Canada. Both fixed and random effects models were used to pool the data across the six studies. The treatment response was measured as the difference between the urinary tract symptoms at baseline versus those at 3, 12, 24, 36, and 48 months after therapy. The treatment response included changes in the American Urological Association Symptom Score (AUA symptom score), peak urinary flow rate in milliliters per second (Qmax), and quality of life (QOL).

Results. The baseline measures were comparable across the studies. At 3 months, the AUA symptom score had improved by a mean of 11.6 (55%), Qmax by a mean of 4.0 (51%), and QOL by a mean of 2.3 (53%). These changes persisted with only slight attenuation through 48 months (corresponding mean changes of 43%, 35%, and 50%). These changes were highly statistically significant ($P < 0.0001$ to 0.01). An improvement of at least 25% was achieved for the AUA symptom score and QOL by more than 85% of men and by more than 65% of men for Qmax.

Conclusions. This pooled analysis of six multicenter studies of cooled thermotherapy, involving 541 men, found highly significant improvements in AUA symptom score, Qmax, and QOL. The results were highly consistent across the studies. The improvements reflected changes from baseline values of 45% to 50% for AUA symptom score and QOL and 35% to 40% for Qmax at a follow-up duration up to 48 months after therapy. The level of improvement for all three measures remained high at 48 months, indicating that the response is durable. UROLOGY **63:** 716–721, 2004.

Lower urinary tract symptoms (LUTS) as a result of benign prostatic hyperplasia (BPH) represent one of the most common medical problems associated with aging in Western men, estimated to afflict approximately 25% of men aged 50 to 79 in the United States.[1] Transurethral microwave thermotherapy (TUMT) is among a number of minimally invasive techniques for treating BPH, as a means of avoiding some of the morbidity, side effects, or high cost associated with surgical or medical therapies. TUMT requires only a single outpatient visit and the use of only oral and local medications. A number of different systems have been developed for the delivery of TUMT; their efficacy and acceptability can vary according to de-

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vice design, protocols used, and intraprostatic temperatures achieved.

The Targis cooled thermotherapy system is a third-generation microwave thermotherapy technology that uses water cooling to protect the urethra and bladder neck and both urethral and rectal temperature monitoring. This thermotherapy technology has been in use for more than 7 years, with more than 50,000 patients treated worldwide. It has shown improved results at 18 months after treatment compared with alpha-blockers[2] and has demonstrated durable improvement in symptoms and quality of life (QOL) for 2 or more years.[3] However, most studies have had limited enrollment and have involved either single institutions or institutions from within a single country. To obtain more broadly representative measures of the effect of the Targis TUMT device on the symptoms of BPH and the durability of response, we performed a pooled analysis of well-designed multicenter studies with at least 4 years of post-treatment follow-up in the United States, Canada, and England.

MATERIAL AND METHODS

Patients

Patients provided informed consent and were enrolled in six institutional review board-approved multicenter studies involving 15 centers in the United States, Canada, and England. All treatments were delivered during 1993 to 1999. Three of the studies were nonrandomized, single-arm trials of TUMT[4,5] and three studies were two-arm trials of standard 60-minute TUMT versus shortened (28.5 minutes) TUMT,[6] transurethral resection of the prostate (TURP),[6] or sham treatment.[7] For each of the two-arm trials, only the 60-minute TUMT arm was included in this pooled analysis. The eligibility criteria included age 45 to 85 years, American Urological Association Symptom Score (AUA symptom score) of 9 or greater, and a mean preprostatic urethral length of 3 to 5 cm. Eligibility criteria also included a peak flow rate (Qmax) of 15 mL/s or less with a voided volume of 125 mL or more.

Treatment

The Targis cooled thermotherapy system consists of a microwave energy generator, a treatment catheter to deliver the energy to the prostate in a targeted fashion and measure urethral temperatures, a rectal temperature sensor, and a water-filled coolant bag that circulates chilled water through the catheter to protect the urethra and bladder neck (Urologix, Minneapolis, Minn). The system achieves intraprostatic temperatures >45°C, which are sufficient to produce coagulation necrosis.[8] Treatment was delivered in an outpatient setting primarily using local anesthesia to the urethra and local medications, although some patients required intramuscular and/or intravenous medication. Patients were able to leave the clinic after the procedure.

Treatment Response

The treatment response was measured using AUA symptom score, Qmax, and QOL. The latter was determined on the basis of the response to a question concerning how men would feel if their current prostate symptoms would continue indefinitely.[9] The baseline measures were compared with the results at 3, 12, 24, 36, and 48 months after treatment.

Statistical Analysis

Paired *t* tests were used to compare the mean change between the baseline and post-treatment values. The data were pooled across studies as the weighted mean of the change from baseline, using inverse variance weights. A random effects model[10] was used when significant heterogeneity was evident across the studies in the mean change at a particular point. Because the results at 2 through 4 years after treatment were available for a smaller subset of patients than for the earlier points, we compared the results at 1 year among those who did and did not have data available in the later years. Chi-square tests of association and relative risks (RRs) with 95% confidence intervals (CIs) were used to correlate the baseline predictor variables with the post-treatment response (all variables dichotomized). All analyses were performed using Statistical Analysis System software (SAS Institute, Cary, NC).

RESULTS

A total of 541 men were included in the pooled analysis (391 from the United States, 97 from England, and 53 from Canada). Most men had previously received medical therapy for LUTS. At baseline, patients had a mean age of 66.3 ± 9.21 years (range 48 to 85), mean prostate-specific antigen (PSA) level of 3.8 ± 4.07 ng/mL (range 0.1 to 36.1), and a mean prostate volume of 42.1 ± 20.00 cm^3 (range 7.2 to 148.2). No statistically significant differences were found in patient age across the six studies. However, one study had a significantly greater baseline PSA level and prostate volume than the other studies (combined), 5.7 versus 3.5 ng/mL and 54.7 versus 41.0 cm^3 ($P = 0.0041$ and $P = 0.0002$, respectively).

TUMT was associated with highly significant changes in all three response measures. Each measure of LUTS improved by about 50%. The percentage of men achieving at least a 50% improvement was 47% to 66% for AUA symptom score, 37% to 46% for Qmax, and 60% to 67% for QOL (the percentages varied with the time measured from 3 months to 4 years). Improvement in these symptoms remained very stable through 4 years, with improvement diminishing slightly between 24 and 48 months (Table I).

As is evident in Table I, follow-up data at 2, 3, and 4 years were available for a smaller subset of the patients than for the earlier follow-up times. This raised the possibility that some patients did not remain under observation because they did not obtain a satisfactory level of improvement from the treatment. This could lead to an optimistic bias to the results based on those who did remain under observation. To evaluate this, we compared the results at 1 year among patients who did and did not have data available at 2, 3, and 4 years.

Table II shows that patients who lacked data at 2, 3, or 4 years had a significantly smaller improve-

TABLE I. *AUA symptom score, peak flow, and QOL indexes at baseline and after treatment to 48 months: pooled data from six multicenter studies of cooled thermotherapy*

Response Indicator	Sample Size (No. of Studies)	Mean	Mean Change (% of Baseline)	95% CI	*P* Value (vs. Baseline)
AUA score					
Baseline	540 (6)	20.91			
3 mo	519 (6)	9.15	−11.57 (55.3)	−12.20, −10.93	<0.00001
1 yr	458 (6)	9.49	−11.42 (54.6)	−12.09, −10.75	<0.00001
2 yr	316 (6)	9.60	−11.02 (52.7)	−12.06, −10.00	<0.00001*
3 yr	229 (4)	11.56	−10.42 (49.8)	−11.40, −9.44	<0.00001
4 yr	171 (3)	11.54	−8.93 (42.7)	−11.05, −6.81	0.0004*
Peak flow (Qmax)					
Baseline	524 (6)	7.91			
3 mo	495 (6)	11.96	4.01 (50.7)	3.57, 4.44	0.00001
1 yr	438 (6)	11.53	3.56 (45.0)	3.11, 4.02	0.00002
2 yr	196 (5)	11.10	3.35 (42.4)	2.70, 4.00	0.0002
3 yr	142 (2)	10.96	3.41 (43.1)	1.72, 5.10	0.011*
4 yr	67 (1)	10.94	2.77 (35.0)	1.72, 3.83	0.00001
QOL					
Baseline	539 (6)	4.29			
3 mo	375 (5)	2.06	−2.28 (53.1)	−2.50, −2.07	<0.00001*
1 yr	456 (6)	1.81	−2.39 (55.7)	−2.53, −2.25	<0.00001
2 yr	315 (6)	1.83	−2.33 (54.3)	−2.60, −2.05	0.00002*
3 yr	229 (4)	2.03	−2.08 (48.5)	−2.40, −1.77	0.00005*
4 yr	171 (3)	1.93	−2.15 (50.1)	−2.74, −1.55	0.0009*

KEY: AUA = American Urological Association; CI = confidence interval; Qmax = peak urinary flow rate; QOL = quality of life.
** Based on random effects model.*

TABLE II. *Comparison of response 1 year after TUMT for subjects with and without follow-up data for years 2 through 4*

Data Availability	Mean Change at 1 yr: Absolute Change (Percent Change) [n]		
	AUA Score	Qmax	QOL
2 yr available	−12.04 (57.6) [312]	4.44 (56.1) [191]	−2.54 (59.2) [309]
2 yr lacking	−9.79 (46.8) [146]	2.95 (37.3) [247]	−2.10 (49.0) [147]
P Value*	0.0057	0.0017	0.0060
3 yr available	−12.73 (60.9) [225]	4.81 (60.8) [138]	−2.59 (60.4) [223]
3 yr lacking	−9.95 (47.6) [233]	3.04 (38.4) [300]	−2.22 (51.7) [233]
P Value*	<0.0001	0.0005	0.0119
4 yr available	−13.11 (62.7) [169]	5.65 (71.4) [64]	−2.62 (61.1) [167]
4 yr lacking	−10.27 (49.1) [289]	3.25 (41.1) [374]	−2.27 (52.9) [289]
P Value*	<0.0001	0.0003	0.0206

KEY: TUMT = transurethral microwave thermotherapy; other abbreviations as in Table I.
** t test comparing mean values for those with data available at given point vs. those lacking such data.*

ment than those who did have data available. Those lacking follow-up data at 2 through 4 years exhibited improvement at 1 year of 46% to 53% for AUA symptom score and QOL and 37% to 41% for Qmax. This compares with a 56% to 71% improvement for all three measures in those who did have available data at 2 through 4 years. Compared with the percentage of improvement shown in Table I, it suggests that the observed improvement at 2 through 4 years is likely to overstate the level for all patients by 5% to 10%. This suggests that the true improvements at 2 through 4 years are likely to be 45% to 50% for AUA symptom score and QOL and 35% to 40% for Qmax. Thus, although the long-term follow-up scores in Table I are likely somewhat optimistic, it is still probable that the average reduction in symptoms of LUTS declines only slightly from 1 through 4 years, suggesting a highly durable response. No statistically significant differences were noted in baseline age, PSA level, prostate volume, AUA symptom score, or Qmax among those with and without long-term follow-up (data not shown). The baseline QOL was significantly worse among those lacking long-term follow-up

(4.37 versus 4.15, $P = 0.0167$), although this difference was small and unlikely to represent a clinically relevant difference. Thus, there is little evidence that individuals lacking long-term follow-up data were those with more resistant disease.

We considered whether any characteristics were able to predict unsatisfactory (less than 25%) versus satisfactory (25% or more) improvement in each of the LUTS outcomes at 1, 2, 3, or 4 years. Potential predictors included baseline characteristics that may represent a greater risk of LUTS (ie, age 65 years or older, PSA level 4.0 ng/mL or greater, and prostate volume 40 cm^3 or greater, as well as an unsatisfactory response to treatment at 3 months).

A PSA level of 4 ng/mL or greater was the only baseline factor associated with an unsatisfactory change, predicting a 60% to 70% increase in the probability of both unsatisfactory AUA symptom score at 4 years (RR = 1.70, 95% CI 1.07 to 2.70, $P = 0.0250$) and Qmax at 3 years (RR = 1.61, 95% CI 1.11 to 2.33, $P = 0.0116$). None of the three baseline factors was significantly associated with the change in any outcome at 1 or 2 years or with QOL at any time. Unsatisfactory improvement at 3 months (less than 25%) was significantly associated with a more than threefold increase in the probability of an unsatisfactory longer term outcome for all LUTS, at all points 1 year or more, except for QOL change at 4 years (data not shown).

Additionally, we examined the failure to sustain an initial satisfactory response. Among patients who had a satisfactory response at 1 year, the proportion that subsequently had unsatisfactory AUA symptom score, Qmax, and QOL at 2 years was 12%, 29%, and 10%, respectively. For these patients, no factors predicted failure to sustain improvement in AUA symptom score or QOL. However, patients with a PSA level of 4 ng/mL or greater were significantly more likely to exhibit a loss of satisfactory response in Qmax (RR = 1.86, 95% CI 1.09 to 3.16, $P = 0.022$).

TUMT produced relatively small changes in PSA and prostate volume. At 12 months after treatment (the only point at which both of these variables were measured in most patients), the mean change from baseline for PSA was −0.27 ng/mL ($P = 0.150$), and for prostate volume, the change was −3.80 cm^3 ($P = 0.0015$). This suggests that the prostate remains largely intact and functional after TUMT.

COMMENT

This multicenter, multinational study of TUMT observed substantial, statistically significant, long-term improvements in AUA symptom score, Qmax, and QOL. Scores improved by an average of approximately 50% at 12 months after treatment and diminished only slightly through 4 years of follow-up, indicating that the treatment response was durable. At 4 years after therapy, a more than 50% improvement was exhibited by 54%, 39%, and 63% of patients for AUA symptom score, Qmax, and QOL, respectively. A satisfactory level of improvement (at least 25%) was observed at all points in more than 85% of patients for AUA symptom score and QOL and in more than 65% of patients for Qmax. To our knowledge, this is the largest series to date of TUMT patients with the longest follow-up. Insufficient numbers of patients with long-term follow-up is a common problem among studies of minimally invasive therapies for BPH, suggesting the possibility that results are optimistically biased through the loss of patients with less than satisfactory outcomes. However, this study had sufficient numbers of patients with 2 or more years of follow-up to evaluate the likely impact of such a bias. The comparison of the level of improvement at 1 year in patients who did and did not have data available for subsequent years suggests that the overall long-term changes are likely to be only slightly smaller than those presented here. Thus, the long-term results observed in this study are a valid indicator of the response in patients with BPH in general.

Improvement occurred in all subgroups of patients, regardless of age, PSA level, or prostate volume. A PSA level of 4 ng/mL or greater was associated with a significantly greater probability of an unsatisfactory response in AUA symptom score and Qmax; however, this was only observed at 3 years or longer after treatment. Despite this statistically significant association, it is necessary to identify additional predictors of unsatisfactory response because approximately 50% of men with a PSA level of 4 ng/mL or greater subsequently achieved a satisfactory long-term response in AUA symptom score and Qmax. A PSA level of 4 ng/mL or greater was also associated with a failure to sustain an initial (1 year) satisfactory response in Qmax. These results suggest that patients with elevated baseline PSA levels may need more careful long-term follow-up to assess the need for retreatment. PSA has previously been shown by one of us (C.G.R.) to be a strong predictor of a deterioration in symptoms and flow rate,[11] episodes of acute urinary retention,[12,13] and prostate growth.[14] However, we believe this is the first time that PSA has been observed to predict subsequent failure in patients who initially exhibited a satisfactory response.

Despite the significant correlation between the 3-month and long-term response, a large proportion of men with an unsatisfactory response at 3 months subsequently exhibited a satisfactory long-

term response, underscoring that it may take more than 6 months to observe the maximal clinical benefit of TUMT. A randomized trial of neoadjuvant and adjuvant alpha-blockade combined with TUMT demonstrated highly significant improvement in symptoms as early as 2 weeks after therapy compared with TUMT alone. That trial only followed up patients for 12 weeks, at which time the two groups exhibited comparable symptom reduction. If these early results of combination treatment were maintained for the long term, it may improve patient satisfaction with TUMT by allowing earlier relief from symptoms.[15]

Because this was not a controlled trial, it is possible that some patients overstated improvement in subjective outcomes such as AUA symptom score and QOL, simply because they knew they had undergone treatment (ie, the placebo effect). Evidence to support this is shown, in this study and in most studies of minimally invasive therapies, that improvement in reported symptoms is greater than that in flow rate. In a randomized trial to compare watchful waiting with TURP, the watchful waiting patients reported more than 35% improvement in symptoms but no improvement was found in the flow rate.[16] Another randomized trial compared TUMT with both sham treatment and a no-treatment control, with both patients and physicians unaware of the TUMT versus sham groups. That study used a different, lower energy/lower temperature microwave device than the one in the current study. No improvement in flow rate occurred in any arm, but similar levels of symptom improvement in the TUMT and sham arms occurred compared with no improvement in the control arm.[17] However, this study differed from most studies of TUMT in that eligibility was strictly limited to patients with urodynamically proven bladder outlet obstruction.[18] To evaluate whether symptom improvement in the current multicenter study is likely to be overstated because of a placebo effect, we examined the long-term improvement in those patients who reported a satisfactory response at 3 months. At 1 year, 90% and 72% of these patients reported satisfactory improvement in AUA symptom score and Qmax, respectively. At 4 years, the corresponding proportions were 73% and 57%, representing a decrease of 19% and 21%, respectively. Because the percentage of reduction was similar, and because the symptomatic improvement remained high at 4 years, it is unlikely that a placebo effect played a major role in the observed responses in this study.

This large, long-term pooled analysis confirms the results observed for TUMT in smaller and shorter term studies.[2,3,7,8] In direct comparison, TUMT has also been shown to compare favorably with medical therapy. In a trial of 103 patients with BPH randomized to TUMT versus alpha-blockade using terazosin, the results at 18 months showed significantly greater improvement with TUMT. The level of improvement with TUMT was 35% greater for the International Prostate Symptom Score, 22% greater for Qmax, and 43% greater for QOL.[2] Few trials have directly compared TUMT with other minimally invasive procedures,[19] although short-term studies of individual procedures suggest fairly similar improvement in symptoms and flow rate.[18] Improvement is not as great as with TURP but is also associated with a lower profile of complications.[20] However, only TUMT can generally be performed using only local and oral medications with minimal patient monitoring.[18] TUMT has a lower frequency of hemorrhage than TURP or other minimally invasive therapies but may require longer catheter duration. Both TUMT and transurethral needle ablation can be performed in an outpatient setting. The rates of retrograde ejaculation are substantially lower than with TURP or transurethral vaporization of the prostate.[21] Cost-effectiveness analysis has suggested that TUMT has lower costs and higher utility than TURP[22]; similar analyses and, especially, evaluation of long-term outcomes are needed for other minimally invasive therapies. Thus, TUMT produces durable relief from LUTS associated with BPH, with favorable cost, a lower side-effect profile, and simpler treatment delivery than other minimally invasive therapies for BPH.

CONCLUSIONS

This pooled analysis of six multicenter studies, involving 541 men, represents the largest series to date of men treated with cooled thermotherapy with the longest follow-up. The study found highly significant improvements in AUA symptom score, Qmax, and QOL. At 1 year post-treatment all three scores had improved by 45% to 50% compared to baseline levels, and at 4 years after treatment improvement remained high at 35% to 50%. The analysis showed that there was likely to be only a slight bias due to selective dropout of men who did not have a satisfactory response to treatment, and that this did not affect the validity of the improvement through 4 years. These results support the use of cooled thermotherapy as effective, durable treatment for the symptoms of LUTS.

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