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**CLINICAL INVESTIGATION** **Prostate**

# PROPHYLACTIC TAMSULOSIN (FLOMAX) IN PATIENTS UNDERGOING PROSTATE $^{125}$I BRACHYTHERAPY FOR PROSTATE CARCINOMA: FINAL REPORT OF A DOUBLE-BLIND PLACEBO-CONTROLLED RANDOMIZED STUDY

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**Purpose: To evaluate the effectiveness of prophylactic tamsulosin (Flomax) in reducing the urinary symptoms in patients undergoing $^{125}$I prostate implantation (PI) for prostate adenocarcinoma.**

**Methods and Materials: This is a single-institution, double-blind, placebo-controlled, randomized trial for patients undergoing PI for prostate adenocarcinoma comparing prophylactic tamsulosin versus placebo. Eligibility criteria included patients not taking tamsulosin or other $\alpha$-blockers treated with PI. The patients were randomly assigned to either tamsulosin (0.8 mg, orally once a day) or matched placebo. All patients started the medication 4 days before PI and continued for 60 days. The American Urologic Association (AUA) symptom index questionnaire was used to assess urinary symptoms. The AUA questionnaire was administered before PI for a baseline score and weekly for 8 weeks after PI. Patients were taken off the study if they developed urinary retention, had intolerable urinary symptoms, or wished to discontinue with the trial.**

**Results: One hundred twenty-six patients were enrolled in this study from November 2001 to January 2003 (118 were evaluable: 58 in the tamsulosin arm and 60 in the placebo group). Pretreatment and treatment characteristics were comparably matched between the two groups. The urinary retention rate was 17% (10 patients) in the placebo group compared with 10% (6 patients) in the tamsulosin group ($p = 0.3161$). Eighty-eight percent (14 patients) of those who developed urinary retention experienced it within 2 weeks after the PI. Intolerable urinary symptoms were reported equally (10 patients in each group) with 70% occurring in the first 2 weeks after PI. There was a significant difference in mean AUA score in favor of tamsulosin at Week 5 after PI ($p = 0.03$).**

**Conclusions: Prophylactic tamsulosin (0.8 mg/day) before prostate brachytherapy did not significantly affect urinary retention rates, but had a positive effect on urinary morbidity at Week 5 after PI.** © 2005 Elsevier Inc.

**Prostate carcinoma, Brachytherapy, Urinary morbidity, $\alpha$-Blockers, Tamsulosin.**

## INTRODUCTION

Adenocarcinoma of the prostate is currently the second most commonly diagnosed cancer in men in the United States and is the second leading cause of cancer mortality (1). In the last decade, owing to outcomes comparable with prostatectomy and external beam radiation therapy (2, 3), there has been an increased interest in treating early-stage prostate cancer with permanent radioactive seed implantation (PI).

After PI, almost all patients develop some degree of urinary irritative or obstructive symptoms, with 3–34% of patients developing acute urinary retention (4–7). Alpha-blockers are widely used either prophylactically or therapeutically to ameliorate these urinary symptoms after the PI (4, 8). No prospective randomized data, however, are available regarding their benefits with PI.

The purpose of this study is to evaluate the effectiveness of prophylactic tamsulosin (Flomax) in reducing urinary symptoms for patients after receiving PI in the setting of a prospective, randomized, double-blind, placebo-controlled study.

## METHODS AND MATERIALS

This is a single-institution, double-blind, placebo-controlled, randomized trial comparing tamsulosin versus placebo for patients

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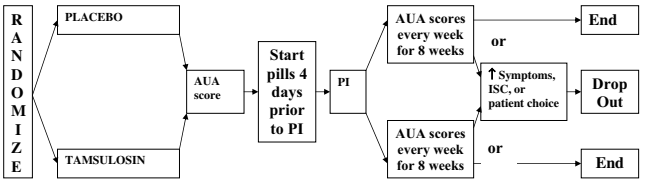


Fig. 1. Schematic representation of the study design and randomization procedure. (AUA = American Urological Association; ISC = intermittent self-catheterization; PI = $^{125}$I prostate implant.)

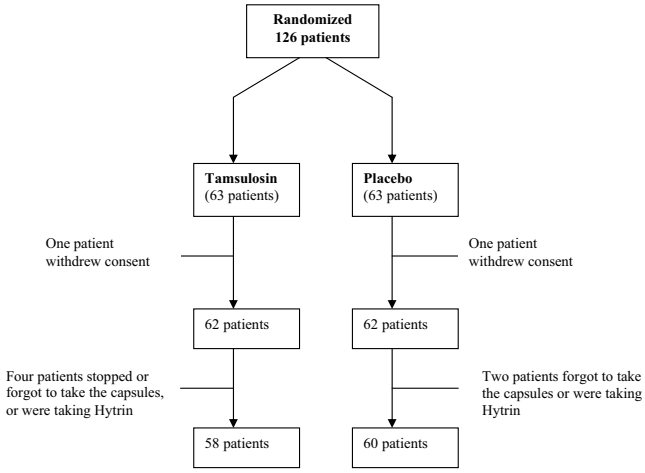


Fig. 2. Diagrammatic representation of the fate of the 126 randomized patients.

undergoing PI for biopsy-proven adenocarcinoma of the prostate. Our Institutional Review Board approved this study. The study schema is illustrated in Fig. 1. Eligibility criteria include patients who chose PI as a treatment option (i.e., patients with low or intermediate-risk prostate cancer), were not taking tamsulosin or other $\alpha$-blockers before PI, had no known hypersensitivity to tamsulosin, could give informed consent, and were >18 years of age. Excluded were those patients with known allergy to tamsulosin and those already taking it or another $\alpha$-blocker before PI. Dexamethasone or other systemic steroids were not allowed during the study period.

Patients underwent standard evaluation preimplant procedures, including complete history and physical examination. Patients were randomized after meeting the eligibility criteria and signing the informed consent. After randomization, the patients were given two bottles containing either capsules of tamsulosin or placebo. The placebo and tamsulosin capsules were identical in size, color, and taste. Patients were unblinded only when they reached the endpoint of the study (intolerable urinary symptoms, or retention of urine requiring self-catheterization [ISC]). Unblinded patients were given the appropriate medications according to their symptoms. There was no crossover between study groups.

As steady plasma level is reached on the fifth day of oral daily use of tamsulosin (9), the patients were instructed to start the study medications 4 days before PI. All the patients were contacted 4–5 days before the procedure to remind them to start the study medication.

All the patients underwent transrectal ultrasound (TRUS)-guided transperineal radioactive seed implantation using a single brand of $^{125}$I sources (Rapid strand; Amersham, Chicago, IL). Isotope implantation was performed by standard technique, using a peripheral loading pattern and according to American Brachytherapy Society guidelines (10). One physician (J.P.C.) performed 98% of the procedures. The minimal peripheral dose was 144 Gy (TG-43) (11). The doses to the urethra were kept below 150% of the prescribed dose. Cystoscopy was done as clinically indicated (blood seen in the urethral meatus) at the conclusion of the procedure. The patients were discharged home on the same day of the PI without an indwelling urinary catheter. All were taught ISC before the procedure and given appropriate supplies.

Postimplant pelvic computed tomography was obtained 4–6 weeks after the PI using 5-mm spacing between images. One physician (J.P.C.) in a blinded fashion did all the postimplant studies. The contoured images and sources were entered into a Varian Variseed treatment planning system (Varian, Charlottesville, VA). Dosimetric information derived from these studies was used as variables in the outcome analysis.

The American Urologic Association (AUA) symptom index questionnaire was given at baseline and weekly for 8 weeks to assess the severity of urinary symptoms after PI as previously described (9). To maintain consistency, one physician (M.A.E.) contacted all patients on a weekly basis. For the purposes of analysis, the AUA score was broken down into two domains: irritative and obstructive. The analyzed irritative urinary symptoms were nocturia, urgency, and daytime urinary frequency. The obstructive urinary symptoms were force of urinary stream, hesitancy, feeling of bladder emptiness, and straining to start urination.

### *Randomization*

The randomization was performed using alternate assignment of the patient to two parallel groups. There were no stratifications. The patients and physician investigators were blinded to the allotted treatment. All patients received the assigned treatment and the analysis was based on the treatment received.

### *Endpoint definitions*

The primary endpoint of the study was reduction of AUA symptom score. The secondary endpoint was urinary retention defined as any use of urinary catheterization to relieve urinary retention after the first 24 hours after the procedure even for a single time. Patients requiring catheterization on the same day of the procedure for clot retention or as a side effect of anesthesia were not coded as urinary retention (2 patients, 1 in each arm).

Patients were taken off the study prematurely when they reported intolerable urinary symptoms (self-perception), developed urinary retention, or wished to discontinue with the trial (for any reason). No patient discontinued study medication secondary to drug adverse effects.

Boehringer Ingelheim Pharmaceuticals (Ingelheim, Germany) provided the tamsulosin samples. Oncura financially supported the study through an educational grant. Neither company had a role in study design, data collection, data analysis, or in the writing of this report.

### *Statistical analysis*

One hundred twenty-six patients were randomized into the two study arms. Sample size calculations determined that 53 patients in each arm would be needed to detect at least a difference of 4 units in the AUA scores between the two study arms with $\alpha$ equal to 0.05 and power equal to 80%. The standard deviation of the AUA score was estimated from previous AUA scores PI patients at the

Table 1. Pretreatment characteristics for all patients in the study broken down by study groups

| Characteristic | Tamsulosin (Flomax) ($n$ = 58) (% or range) | Placebo ($n$ = 60) (% or range) | $p$ value |
|---|---|---|---|
| Age in years (median) | 64 (44–76) | 66 (44–82) | 0.6245 |
| Race (% African American) | 10 (17%) | 6 (10%) | 0.2507 |
| Median PSA (ng/mL) | 6.4 (2.4–24.1) | 6.1 (1.7–21) | 0.3314 |
| Gleason score | | | 0.9462 |
| 5 | 2 (3%) | 2 (3%) | |
| 6 | 45 (78%) | 48 (80%) | |
| 7 | 11 (19%) | 10 (17%) | |
| AJCC 1997 T stage | | | 0.3797 |
| T1a | — | 1 (2%) | |
| T1c | 49 (84%) | 54 (90%) | |
| T2b | 9 (16%) | 5 (8%) | |
| Androgen deprivation | 5 (9%) | 6 (10%) | 0.9455 |
| Baseline AUA score (out of 35) | Median = 4 (0–15) | Median = 5 (1–13) | 0.7642 |
| Baseline irritative AUA score (out of 15) | Median = 2 (0–11) | Median = 3 (0–11) | 0.2640 |
| Baseline obstructive AUA score (out of 20) | Median = 2 (0–12) | Median = 2 (0–8) | 0.9911 |

*Abbreviations:* AJCC = American Joint Committee on Cancer; AUA = American Urologic Association; PSA = prostate-specific antigen.

Cleveland Clinic Foundation. An additional 20 patients were included to account for potential dropouts.

An interim analysis was planned after 60 patients completed the study. A $p$ value $<0.001$ was used as the monitoring boundary for this interim analysis. This interim analysis showed no significant difference between the two groups.

Repeated measures analysis of variance (ANOVA) was used to determine if there was a significant difference between the mean AUA scores of the two groups over the entire study period, and $t$-tests were used to examine if there was a difference in the AUA scores for the two groups at each week of the study period. The chi-square test was used to determine if there was a difference in the rate of urinary retention or withdrawal due to severe urinary symptoms between the two study groups.

## RESULTS

Between November 2001 and January 2003, 126 patients were enrolled on the study. A total of 118 patients (58 and 60 patients in the tamsulosin and the placebo groups, respectively) were evaluable. See Fig. 2 for a

Table 2. Anatomic, procedural, and postimplant dosimetric variables for the study groups

| Characteristic | Tamsulosin (range) | Placebo (range) | $p$ value |
|---|---|---|---|
| Anatomic | | | |
| Median prostate volume in $cm^3$ | 35.9 (14.0–122.0) | 34 (14–117.0) | 0.3908 |
| Median prostate length in mm | 45 (33–72) | 44 (28–70) | 0.3455 |
| Median prostate width in mm | 50 (22–70) | 48 (33–68) | 0.7013 |
| Median prostate height in mm | 32 (21–75) | 32 (21–57) | 0.2762 |
| Procedural | | | |
| Median number of needles used/patient | 28 (18–52) | 28 (18–48) | 0.3470 |
| Median number of seeds/patient | 110 (70–224) | 102 (56–234) | 0.2692 |
| Median total activity (U) | 46.8 (32.55–101.92) | 43.51 (25.2–108.11) | 0.2132 |
| Prostate dosimetry | | | |
| Median D90* | 147.56 | 148.85 | 0.9220 |
| Median D100 | 76.92 | 76.18 | 0.8546 |
| Median V100† | 91.43 | 91.34 | 0.9645 |
| Median V150 | 56.53 | 56.20 | 0.4159 |
| Median V200 | 26.14 | 31.27 | 0.2670 |
| Median V300 | 8.28 | 8.59 | 0.4850 |
| Median V400 | 4.34 | 4.46 | 0.5169 |
| Urethral dosimetry | | | |
| Median D100‡ | 132.17 | 128.98 | 0.4768 |

* D90: minimal dose received by 90% of the prostate gland.

† V100, 150, 200, 300, 400: percentage of prostate gland volume receiving 100%, 150%, 200%, 300%, and 400% of the prescribed minimal peripheral dose, respectively.

‡ Urethral D100: minimal dose received by 100% of the urethra.

Table 3. Fate of the study patients after randomization

| Fate | Tamsulosin ($n$ = 58) (%) | Placebo ($n$ = 60) (%) | $p$ value |
|---|---|---|---|
| Completed 8 weeks | 42 (72%) | 40 (67%) | 0.7893 |
| Withdrawal due to: | | | |
| Intolerable symptoms | 10 (17%) | 10 (17%) | 0.9337 |
| Urinary retention | 6 (11%) | 10 (17%) | 0.3160 |

breakdown of the 126 randomized patients. Table 1 summarizes the pretreatment characteristics of the 118 evaluable study patients. The two treatment groups were comparably matched for the pretreatment as well as posttreatment characteristics (Tables 1 and 2). None of the patients had a transurethral resection of the prostate (TURP) before PI.

The compliance rate was 100% for the 118 evaluable patients. There was only one reported side effect related to the study drug in the form of ejaculatory failure in the tamsulosin group. Thirty-six patients were taken off the study for various reasons, leaving 82 patients to complete all 8 weeks of the trial (Table 3).

For those patients requiring ISC, the median duration for ISC use was 5 days in the tamsulosin group (range, 1–14 days) compared with 2 days for the placebo group (range, 1–44 days). The difference was not significant. The median time to stopping the trial for those who were removed from the trial was 11 days (range, 1–36). Intolerable urinary symptoms were reported equally in the two study groups. Eighty-seven percent of those who developed intolerant urinary symptoms experienced them within 2 weeks after PI. Sixty percent of those who developed urinary retention experienced it within 2 weeks after PI.

Urinary symptoms were evaluated for the entire study period utilizing repeated measures ANOVA and unpaired $t$-tests for week-by-week comparisons. For the entire study period, there was no difference in the AUA scores between the two groups. At Week 5, tamsulosin significantly reduced the mean AUA symptom score for all patients ($p$ = 0.03), and for those who completed all 8 weeks of the study ($p$ = 0.05; Fig. 3).

With respect to the irritative and obstructive domains of the AUA score, tamsulosin (significantly reduced the mean irritative urinary symptom score at Week 5 after the procedure for all patients ($p$ = 0.02), and for those who completed all 8 weeks of the study ($p$ = 0.03). There was no difference in the mean obstructive urinary symptom score between the two groups for the entire study period or at any specific week.

No significant acute side effects have been noted with the tamsulosin and the side-effect profile was in agreement with the previously published studies (only 1 patient in the tamsulosin group reported ejaculatory failure).

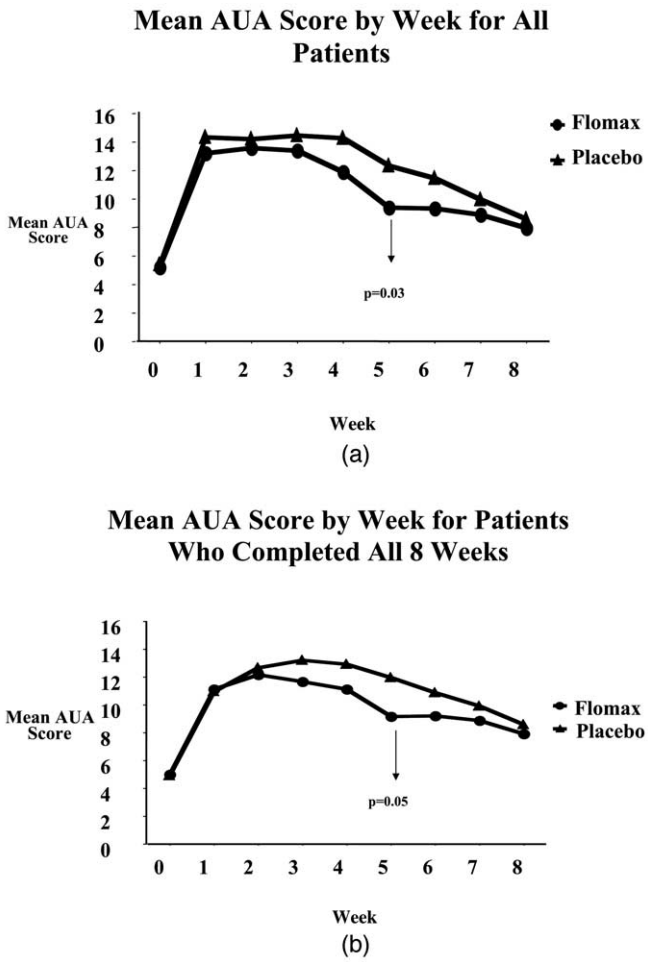


Fig. 3. (a) Graphic depiction of the mean American Urological Association (AUA) symptom scores over the course of the trial for all 118 evaluable study patients. Fifty-eight were on the Flomax arm and 60 were on the placebo arm. There was a significant difference at Week 5 in favor of the patients receiving Flomax ($p$ = 0.03). (b) Graphic depiction of the mean AUA symptom scores for the 82 patients who completed all 8 weeks of the trial. Forty-two were on the Flomax arm and 40 were on the placebo arm. There was a significant difference at Week 5 in favor of the patients receiving Flomax ($p$ = 0.05).

## DISCUSSION

The efficacy of PI in treating prostate cancer is being shown to be on a par with the major competing modalities (2). As a result, investigations seeking to discriminate among therapeutic approaches will need to focus on toxicity: not only trying to understand its incidence but also attempting its amelioration. The present study illuminates both of these aspects of toxicity.

The implantation technique applied in this trial deviates slightly from those employed in other institutions in two important ways. First, we perform all planning during the same anesthesia session as the implantation, resulting in superior postimplant dosimetry relative to a two-step preplanning technique (12). Second, since there is no patient manipulation without anesthesia, we do not employ a pros-

tate size constraint on eligibility for the procedure. This technique eliminates significant pubic arch interference. Regardless of the differences, for within-trial comparative purposes, the patient groups were evenly matched (Tables 1 and 2).

We found the timing of peak urinary morbidity to be at Weeks 2–3. This finding is somewhat confirmed by other work (13) and refuted by some (14). The aforementioned works may differ from this study, because they did not examine the urinary morbidity as frequently as it has been done here. We performed our assessments at weekly intervals while the aforementioned investigators used more protracted schedules.

The different definitions of urinary retention after PI may be the reason for the wide range of retention rates after PI. Terk *et al.* (15) defined it as urinary retention that required urinary catheterization for more than 2 days. On the other hand, Kang *et al.* (16) defined it as the use of urinary catheterization for more than 1 week. The definition of urinary retention employed here (the use of urinary catheterization even for a single use not related to clot retention or anesthesia effect) is more reproducible and we felt that it was more easily applied clinically. As a result of the definition differences, as well as the retrospective nature of the previously mentioned works, the ISC rates reported here may differ. Within the trial, the same definition was used and no differences were found between the two groups.

An interesting finding of the trial is Flomax's apparent focus on reducing irritative urinary symptoms. We found this to be unexpected, because Flomax affects $\alpha$-receptors and should show more activity in the obstructive domain of the AUA score. This may be explained by the notion that $\alpha$-blockade may also reduce hyperactivity of the trigone and therefore lyse the cascade of events leading to generalized bladder irritability. In addition, the lack of an effect on the obstructing symptoms may reflect the overriding effect of prostate edema on obstruction. This last hypothesis is currently being tested in a succeeding protocol.

Regardless of the positive nature of the trial, it does not completely solve the problem of postimplant morbidity. The patients receiving Flomax did not show a reduction in AUA symptom score at all time intervals. The difference was confined to Week 5. This may be explained in several ways. The finding may be totally spurious. It may be due to the need for a longer preimplantation dosing regimen or, as stated previously, the overriding effect of prostate edema. The possibility of the result being false is real, but the AUA symptom scores do show a trend over all time intervals except Weeks 1 and 2 in the direction of the result and this is hard to ignore. Our feeling is that the overriding effect of prostate edema is the better explanation, because prostate edema is usually resolving itself with the same time frame. As a result, we will test the addition of an anti-inflammatory to Flomax in the successor trial. This trial is accruing patients as of the writing of this article.

## CONCLUSION

In conclusion, this study demonstrates that prophylactic tamsulosin (Flomax) has a positive impact on urinary symptoms at Week 5 after PI. A follow-up study, currently under way, will test the hypothesis that reducing prostate edema associated with the procedure in addition to an $\alpha$-blocker may further improve urinary symptoms after prostate brachytherapy.

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