THE ROLE OF PROPHYLACTIC TAMSULOSIN (FLOMAX®) ± DEXAMETHASONE IN PATIENTS UNDERGOING PROSTATE I^{125} SEED IMPLANTS FOR PROSTATE CARCINOMA: A RANDOMIZED DOUBLE-BLIND STUDY

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ABSTRACT

Introduction: **In this study, we aimed to evaluate the effectiveness of prophylactic dexamethasone added to tamsulosin (Flomax®) in reducing urinary symptoms after I^{125} prostate brachytherapy (PI) for prostate adenocarcinoma.**

Materials and Methods: **A single institution, randomized, double blind, placebo controlled trial of patients undergoing PI for prostate adenocarcinoma comparing the use of prophylactic dexamethasone plus tamsulosin before PI versus placebo plus tamsulosin was conducted. Patients undergoing permanent PI, who were not taking tamsulosin or other alpha-blockers prior to PI were eligible for the trial. All patients were given tamsulosin (0.8 mg, orally once a day) and were randomized to receive either placebo or dexamethasone (4 mg per day for the first 10 days after PI and then 2 mg per day for 4 additional days). Tamsulosin use was started four days prior to PI and continued for 60 days. Urinary symptoms were assessed with the American Urologic Association (AUA) symptom index score. The questionnaire was administered prior to PI and then on a weekly basis for the first eight weeks after PI and again at weeks 10 and 12 after PI. The primary endpoint of the trial was change in the AUA score from baseline. Patients were taken off of the study if they developed urinary retention, had intolerable urinary symptoms, or wished to discontinue with the trial.**

Results: **One-hundred patients were enrolled in the study. Ninety-four patients started the study and 72 completed all 12 weeks. Patients were evenly matched according to pre-treatment and post-treatment characteristics except with regard to pre-treatment AUA score: the dexamethasone group had a median score of 3 while the placebo group had a median score of 5 (p=0.0023). When comparisons were made between the groups relative to percent change in overall AUA score from baseline, there was a significant difference in favor of the placebo group (p=0.0030).**

Conclusion: **The combination of prophylactic dexamethasone and tamsulosin yields worse post-operative symptoms than prophylactic tamsulosin alone.**

Key words: **Adenocarcinoma, Brachytherapy, Dexamethasone, Prostate, Tamsulosin**

ÖZET

Biz bu çalışmada prostat adenokarsinomu nedeniyle I^{125} ile brakiterapi yapılan hastalarda üriner belirtileri azaltmak amacıyla kullanılan tamsulosine deksametazon eklenmesinin proflaktik etkilerini değerlendirmeyi amaçladık.

Tek merkezli, randomize, çift-kör, plasebo kontrollü bu çalışmada prostat adenokarsinomu nedeniyle brakiterapi yapılan hastalarda brakiterapi öncesi uygulanan deksametazon+tamsulosin tedavisi ile plasebo+tamsulosin tedavisi sonuçları karşılaştırıldı. Çalışmaya, prostat kanseri nedeniyle brakiterapi uygulaması yapılan ve daha önce tamsulosin veya başka alfa bloker tedavisi almayan hastalar alındı. Günlük doz 0,8 mg olarak tamsulosin başlanmasının ardından tüm hastalar plasebo ve deksametazon (brakiterapiden sonra 10 gün süreyle 4 mg/gün, sonraki 4 gün için 2 mg/gün) alacak şekilde randomize edildi. Tamsulosin brakiterapiden 4 gün önce başlandı ve toplam 60 gün kullanıldı. Semptomlar AUA semptom skoru ile değerlendirildi. Semptom skoru brakiterapi öncesi ve brakiterapi sonrası 8 hafta süreyle haftada bir kez, sonrasında 10. ve 12. haftalarda bakıldı. Çalışmanın birincil son noktası başlangıç değerlerine göre AUA skorundaki değişiklik olarak belirlendi. İdrar retansiyonu veya tolere edilmeyecek düzeyde belirtileri olan veya çalışmaya devam etmek istemeyen hastalar çalışmadan çıkarıldı.

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Çalışmaya alınması planlanan 100 hastadan ancak 94 tanesi çalışmaya başladı. Altı hasta değişik nedenlerle brakiterapi uygulamasından vazgeçtiler. Kalan 94 hastanın ise 72'si 12 haftayı tamamlayabildi. Hastalar tedavi öncesi ve tedavi sonrası karakteristikleri benzer olmasına karşın sadece tedavi öncesi AUA skoru deksametazon grubunda ortanca 3 iken plasebo grubunda 5 olarak bulundu (p=0,0023). Gruplar arasında başlangıç AUA skoru temel alınarak yapılan karşılaştırmada plasebo grubu lehine anlamlı değişiklik saptandı (p=0,0030).

Deksametazon ve tamsulosinin birlikte proflaktik kullanımı, tek başına tamsulosin kullanımına göre brakiterapi sonrası belirtileri daha da kötüleştirmektedir.

Anahtar kelimeler: Adenokarsinom, Brakiterapi, Deksametazon, Prostat, Tamsulosin

INTRODUCTION

Permanent prostate brachytherapy (PI) has been shown to be an effective curative therapy for prostate adenocarcinoma (CaP)[1,2]. Given its high rates of biochemical relapse-free survival (bRFS), a logical direction of research is to maintain that efficacy while reducing toxicity. Initial work by our group has demonstrated the significance of prostate anatomy (prostate/urethral length) in predicting urinary morbidity[3]. This finding provided us with an impetus to examine, in a clinical trial, the use of tamsulosin as a prophylactic agent against urinary obstruction. The results of that clinical trial revealed that tamsulosin was somewhat effective but, that its action seemed to be primarily to target the irritative domain of the AUA symptom score rather than the obstructive domain[4]. In an effort to attack the obstructive domain of the AUA score, this trial was conceived. The hypothesis was that the addition of a potent anti-inflammatory such as dexamethasone will reduce the edema after PI and thereby reduce obstructive symptoms.

MATERIALS and METHODS

Design and Eligibility: The study design of this trial is shown in the schema (Figure 1). The goal of the trial was to evaluate the effectiveness of tamsulosin ± dexamethasone in reducing urinary symptoms after PI. Urinary symptoms were assessed with the American Urologic Association (AUA) symptom index score. The primary endpoint was change in the AUA score from baseline measured weekly for eight weeks after PI and at weeks 10 and 12 after PI. The secondary endpoint was to evaluate the effectiveness of tamsulosin± dexamethasone in reducing the rate of intermittent self-catheterization (ISC) after PI. Patients were eligible for the trail if they could give informed consent, had a confirmed diagnosis of CaP, were not taking alpha blockers, were not diabetic, did not have a known hypersensitivity to tamsulosin or dexamethasone, and did not have narrow angle glaucoma. The trial was approved by our IRB.

Brachytherapy: All patients were treated according to the American Brachytherapy Society guidelines using I^{125} in the form of RapidStrand®. A dose of 144 Gy was prescribed as a minimum dose to the entire gland with approximately a 5 mm margin in the anterior and lateral directions. There was no posterior margin. The dose to the urethra was limited to 150% of the prescribed dose or 216 Gy.

Drug Delivery: The tamsulosin dose was 0.8 mg per day, and patients were instructed to take the drug in the evening as a single dose (two capsules). Patients started taking tamsulosin four days prior to the implant to achieve a steady-state plasma concentration prior to PI. Patients continued the tamsulosin for eight weeks after PI. The dexamethasone or a matched placebo was started on the day of PI at a dose of 4 mg per day. This dosage continued for 10 days and was then reduced to 2 mg per day for four additional days. The total duration of dexamethasone or placebo use was14 days.

Endpoint Assessment: A baseline AUA symptom score was taken prior to patients starting any of the study medications and weekly for eight weeks after PI and then at weeks 10 and 12. During the follow-up period, patients were monitored for ISC or excessive elevations of the AUA score. An excessive elevation was defined as a maximum AUA score for more than two consecutive weeks. ISC was defined as any use of the catheter after PI. All patients were instructed on the use of the catheter and given catheters to take home. If a patient exhibited ISC, excessive AUA score elevation, or simply wanted to withdraw they were removed from the trial and standard post-operative care was delivered.

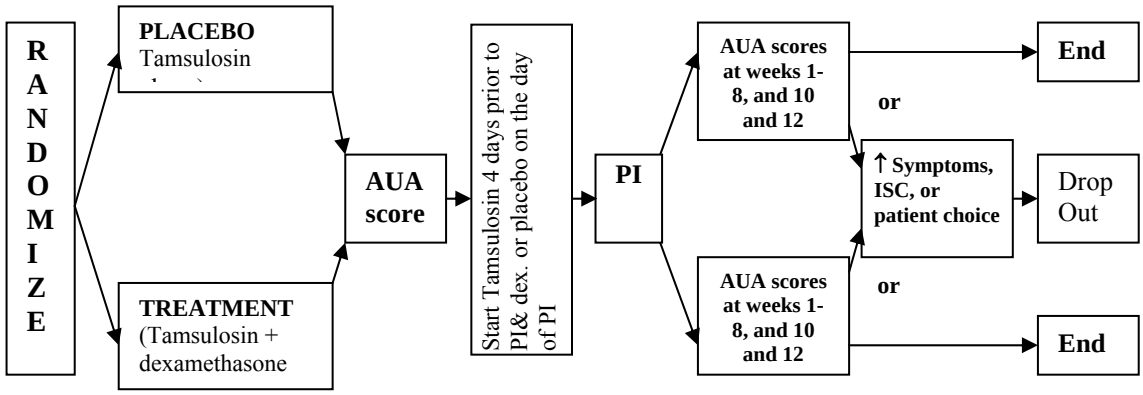

Figure 1. The study's schema indicating the timing of the medications and the randomization technique

Table 1. Pre-treatment patient characteristics

Factor			Group (n)			p value
			All	Tam. + Dex.	Tam. + Plac.	
Bx. Gleason Score		4	2 (2.1%)	1 (2.2%)	1 (2.0%)	0.97
		5	1 (1.1%)	1 (2.2%)	0 (0.0%)	
		6	64 (68.1%)	30 (66.7%)	34 (69.4%)	
		7	27 (28.7%)	13 (28.9%)	14 (28.6%)	
Initial PSA	≤ 10 ng/ml		84 (89.4%)	39 (86.7%)	45 (91.8%)	0.85
	> 10 ng/ml		10 (10.6%)	6 (13.3%)	4 (8.2%)	
Clinical Stage		T1C	75 (79.8%)	37 (82.2%)	38 (77.6%)	0.77
		T2A	15 (16.0%)	8 (17.8%)	7 (14.3%)	
		T2B	3 (3.2%)	0 (0.0%)	3 (6.1%)	
Race		AA	6 (6.4%)	1 (2.2%)	5 (10.2%)	0.11
		W	88 (93.6%)	44 (97.8%)	44 (89.8%)	
Androgen Deprivation		N	87 (92.6%)	43 (95.6%)	44 (89.8%)	0.29
		Y	7 (7.4%)	2 (4.4%)	5 (10.2%)	
Age (years)	Mean		66.3	67.0	65.7	0.41
	Median (range)		67 (47-87)	68 (47-81)	66 (51-79)	
AUA Score	Mean		5.0	3.8	6.1	0.0023
	Median (range)		4 (0-17)	3 (0-11)	5 (0-17)	
Obst. AUA Score	Mean		1.9	1.1	2.6	0.0025
	Median (range)		1 (0-13)	0 (0-7)	2 (0-13)	
Irrit. AUA Score	Mean		3.1	2.7	3.5	0.07
	Median (range)		1 (0-10)	3 (0-7)	3 (0-10)	
Prostate Vol.(cc)	Mean		37.93	38.63	37.29	0.70
	Median (range)		32.4 (14.9-98.3)	37.0 (15.5-98.3)	31.9 (14.9-83.3)	

Statistical Considerations: One hundred patients were randomized equally between the two arms. Assuming a standard deviation of seven for the mean AUA score, it was determined that 48 patients would need to be randomized to each arm to detect a difference of at least four points in the

AUA scores between the two arms with α equal to 0.05 and power equal to 80 percent. To account for potential dropouts, four additional patients were enrolled. The sample size calculations were based on our experience from a similar trial[4].

To adjust for a difference in baseline AUA scores between the two arms, the percent difference from baseline AUA score for each week was calculated using the equation:

[(Week x AUA score + 1) - (Baseline AUA score + 1)] / [Baseline AUA score + 1].

To control for AUA scores of zero, scores were increased by one point.

Repeated measures analysis of variance (ANOVA) was used to determine if there was a significant difference of the mean percent difference of AUA scores between the two groups over the study follow up period.

RESULTS

One-hundred patients were enrolled in the trial. Six patients dropped out of the trial prior to PI for various reasons (3 didn't take the medication as directed, 1 developed shingles prior to PI, 1 elected to have a radical prostatectomy, and 1 decided on watchful waiting) leaving 94 patients to initiate the trial. The pre-treatment patient characteristics are shown in Table 1. The only significant difference between the two arms was in the baseline AUA score. The dexamethasone group had a significantly lower overall median baseline AUA score (3 versus 5, p=0.0023). The difference seemed to be mainly due to worse obstructive symptoms in the placebo group (see Table 1). Patients were evenly matched on all post-operative variables examined including D90 (minimum dose received by 90% of the gland), gland volume, V100 (volume of the gland receiving 100% of the prescribed dose), V400, D100 of the urethra, prostatic length, activety per source, and number of needles used.

Of the 94 patients who entered the trial, 72 (77%) completed all 12 weeks. The reasons for patient attrition while on the trial were ISC use (9 in each group) and severe symptoms (3 in dexamethasone + tamsulosin and 2 in tamsulosin). Severe symptoms were as defined as a patient's wish to withdraw from the trial due to acute urinary toxicity or complications from the study medications. A comparison of the percent difference in AUA scores for the two study arms of the 72 patients completing all 12 weeks of the trial is shown in Figure 2. The tamsulosin + dexamethasone group did significantly worse (p=0.0030). There was no difference in the rate of ISC between the two groups (dexamethasone + tamsulosin: 20%, tamsulosin: 18.4%, p=0.84).

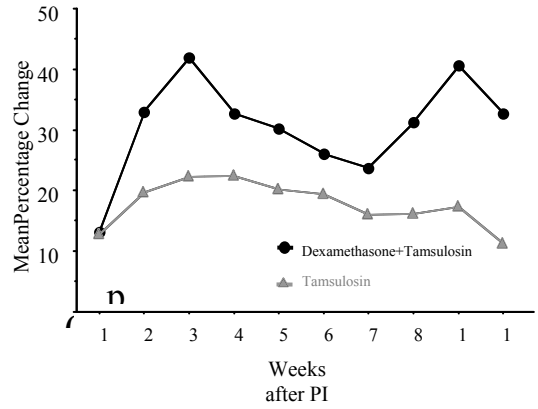

Figure 2. This is a graphic depiction of the AUA score throughout the trial. It is shown as a percent change from baseline with the repeated measure analysis of variance result (p= 0.0030)

Since nearly a quarter of the study population was not able to complete all 12 weeks of the trial, two additional repeated measures ANOVA of percent difference of AUA scores for all 94 patients was done using imputed data for the 22 patients who had to withdraw from the study due to severe symptoms or ISC use. Two sets of imputations were done. For the first imputation patients who withdrew were assigned a maximum AUA score of 35 for the weeks following the patient's withdrawal. For the second imputed data analysis, a mean post PI AUA score from based on the AUA scores prior to the week of patient's withdrawal were calculated. These post PI AUA scores were then assigned as the weekly value of a patient's AUA score following the patient's withdrawal. For both analyses, the tamsulosin + dexamethasone group did significantly worse (p<0.0001 when maximum AUA score used, p=0.0020 when mean AUA score used).

DISCUSSION

The rising popularity of PI[5] calls attention to the need to address its toxicity since its efficacy appears to be well documented. Various publicati-

ons have described the side effect profile of PI quite well[6-10]. It is clear that urinary morbidity after PI consists of both irritative and obstructive symptoms. A previous attempt by our group to reduce these symptoms with the use of tamsulosin met with moderate success[4]. This trial tried to capitalize on those findings by combining tamsulosin with dexamethasone. The hypothesis being that a more effective prophylaxis could be achieved if both the irritative and obstructive aspects of the toxicity profile are addressed.

The results of this trial show two important findings. First, the addition of dexamethasone increases urinary morbidity as determined by the AUA symptom score. Second, the use of dexamethasone did not alter the rate of ISC.

The conclusions of this trial seem to contradict one retrospective study[11] and reinforce another[12]. The differences may be accounted for by the fact that the antecedent works were retrospective while the present study is prospective, double-blinded, and randomized. Additionally, the prior study endpoints are somewhat subjective, which introduces another level of complexity. Our trial was conducted with one person (T.P.C.) administering the AUA symptom score in the hope that such consistency would remove some subjectivity. As a result, we feel that our conclusions are more robust than those of previously reported studies.

One difficulty encountered while analyzing the data was the difference in baseline AUA scores between the two study arms. Because of this, one might suspect that this trial's outcome is the result of differences in baseline AUA scores rather than the post-operative effects of the study medications. The major reason for our contention that this is not the case is that the difference in baseline AUA scores did not result in more patients in the dexamethasone arm reporting maximum AUA scores. Specifically, there were 3 incidence in each study arm where a patient experienced a maximum AUA score. If the difference in baseline AUA score were to significantly affect the outcome, one would expect the "ceiling" of the maximum AUA score to be reached more often in the arm with the higher baseline AUA score. This was not seen. Our solution to the problem was to analyze the data based on percent difference from baseline rather than absolute AUA score.

The ISC rate for this trial appears to differ from our previous work[3,4]. It must be remembered that our definition of ISC is very unforgiving. We require only one use to qualify for the ISC category. This explains the differences between us and most other investigators who often allow ISC in the first week without citing it as an event. The small numbers of patients experiencing the problem in either trial may explain the difference between this trial and our previous trial.

An explanation of these results requires knowledge of the post-operative effects of PI on the gland anatomy. One change that is well documented is that edema after PI resolves within the first few weeks to months[13]. We presumed that the use of dexamethasone would reduce the edema. This presumption is supported by the work of others[14]. With reduced edema there would be an increase in urethral dose since the sources would be closer to the urethra than when the edema is allowed to take its normal course. It may be that this increased urethral dose causes urethritis that would then elevate the AUA symptom score. The work of Wallner et al.[15] support the assumption of a link between source placement and urethral morbidity. Our post-implantation urethral dosimetry does not disclose any such difference. However, our dosimetry was assessed at one month after PI and the edema effect would have resolved by then in the placebo arm. Therefore, one would not expect to see a difference in urethral dosimetry at that time point. Contrary to our initial hypothesis, we feel that edema after PI may be beneficial in reducing urethral dose and minimizing urethritis.

CONCLUSION

The addition of prophylactic dexamethasone and tamsulosin after PI creates more urinary toxicity than prophylactic tamsulosin alone. Also, prophylactic dexamethasone does not affect the rate of ISC after PI. By reducing prostate edema after PI, the use of prophylactic dexamethasone may actually be causing increased urinary morbidity.

KAYNAKLAR

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