A Randomized Clinical Study to Compare the Efficacy and Safety of Naftopidil Versus Tamsulosin in Symptomatic Benign Prostatic Hyperplasia

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ABSTRACT

Aim: To compare the clinical efficacy and tolerability of naftopidil versus tamsulosin in patients with LUTS due to BPH. Tamsulosin acts via α1A-receptor and naftopidil acts via α1D-receptor blocker. The latter is believed to be more efficacious with fewer side effects.

Settings and Design: A prospective, randomized, non-placebo clinical study.

Methods and Materials: 110 patients fulfilling our inclusion criteria were randomized (double-blinded) to receive naftopidil (50 mg) or tamsulosin (0.4 mg) once daily for 3 months after obtaining institutional ethical clearance and administering informed consent. The patients were followed for changes in International Prostate Symptom Score (IPSS), Sexual Function Inventory Score (SFIS), peak flow rate (PFR), average flow rate (AFR), post-void residue (PVR), episodes of acute urinary retention (AUR), and side effects, which were recorded and analyzed using appropriate statistical tools.

Statistical Analysis: Recorded data was analyzed using appropriate statistical tools including the unpaired Student *t* test, Tukey test, and the repeated measure ANOVA test.

Results: Naftopidil and tamsulosin both improved patient symptoms, uroflowmetry, and other parameters. Naftopidil appeared to have an earlier onset of action shown by significant change in values of IPSS ($P = 0.003$), PVR (0.041), storage subscore (SIPSS) ($P = 0.011$), and QoI ($P = 0.017$) at 2 weeks. A higher incidence of postural hypotension, headache, and drug failure were observed with tamsulosin (not statistically significant). SFIS was significantly lower in the tamsulosin group.

Conclusions: The management of symptomatic BPH, with either naftopidil or tamsulosin, appeared to be equally effective, safe, and well tolerated. Naftopidil appeared to have a faster onset of action with fewer side effects versus tamsulosin. All patients appeared to be equally compliant, and there was no treatment withdrawal due to observed side effects with either drug.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a progressive disorder of aging men that is associated with bothersome lower urinary tract symptoms (LUTS) [1]. The vast majority of BPH patients benefit from medical management as an initial therapy, with surgery reserved for select indications. Alpha (α)-blockers with or without 5 α-reductase inhibitors forms the current mainstay of medical management for LUTS due to BPH. It is believed that there is a dominance of α1D-adrenoreceptors (AR) in the prostate and smooth-muscle detrusor in patients with BPH [2].

The safety and efficacy of tamsulosin for LUTS due to BPH is attested by some randomized clinical trials (RCTs) in the

Table 1. The mean initial values of salient patient parameters evaluated in 101 patients form both groups.

Initial Parameters	Naftopidil (N) 50	Tamsulosin (T) 51	P value*
Age	61.69 (48-88)	61.15 (46-78)	0.744
Body mass index	22.106 (18.2-29.1)	21.779 (17-27.8)	0.501
Mean prostate grade (DRE)	1.84	1.95	0.283
Average flow rate (ml/sec)	4.19 (1.2-11.2)	4.434 (1.9-14.3)	0.627
IPSS score	21.06 (10-35)	21.53 (10-35)	0.739
Storage SS of IPSS	10.46 (4-15)	10.49 (4-15)	0.963
Voiding SS of IPSS	10.72 (2-20)	10.75 (2-20)	0.979
Maximum flow rate (ml/sec)	10.62 (3.2-41)	9.41 (4.2-25.4)	0.273
Post void residue (mls)	64.4 (0-246)	72.34 (0-400)	0.549
Quality of life	3.68 (2-5)	3.78 (1-5)	0.46
SFIS**	38.27 (12-44)	38.42 (21-44)	0.927
Flow time (secs)	37.92 (14-70)	34.26 (12-105)	0.265
Hesitancy (secs)	4.934 (0-22)	5.814 (0-18.5)	0.344
Voided volume (CC)	148.02 (39-496)	128.55 (10-294)	0.197
Prostate volume (CC)	31.38 (15-65)	30.01 (18-64)	0.507

*Indicates both groups were similar, P value was not significant; **SFIS evaluated in 61/101 patients only (30 in N vs 31 in T); values in parenthesis represent the range.

be used as an alternative to tamsulosin for patients of LUTS due to BPH; however, there appears to be no published study in the English literature evaluating the efficacy and safety of naftopidil for BPH in the Indian population. This forms the basis for undertaking the current study. This study was conducted to compare the clinical efficacy and tolerability of naftopidil versus tamsulosin in Indian patients with LUTS due to BPH.

SUBJECTS AND METHODS

After obtaining ethics committee clearance and administering informed consent, the current study was conducted from October 2010 to April 2012 from the outpatient clinic of our institution. One hundred and ten eligible patients were consecutively enrolled as per protocol and randomized into 2 groups. The randomization table was generated on September 21, 2010 from http://www.randomization.com. The randomization/allocation of patient group(s) and patient data per protocol was recorded by a resident (second author) who was blinded to the study medication. The protocol, concept, design, and intellectual content for the current study was drafted, conceived, and contributed by the first author who was also blinded to relevant patient data at the time of its interpretation and statistical analysis.

Entry criteria as per protocol included symptomatic patients of BPH with an IPSS score of > 8 or > 3 points for frequency, nocturia, and urgency on IPSS score. Other criteria included patients with persistent bothersome LUTS due to BPH, or a prostate volume > 15 ml, or a peak flow rate of < 10 ml for a voided volume of > 150 ml due to BPH without desiring surgery. Patients with hypersensitivity to α–blockers; a history of prostatic or urethral surgery; those with absolute indications for prostate surgery, neurological disorders, neurogenic bladder, and cardiovascular, renal, or hepatic dysfunction; and those who did not consent their inclusion in this study were excluded. Patients receiving tricyclic antidepressants, anticholinergics, sympathomimetics, 5-ARI, or first-generation antihistamines in the previous 3 months were also excluded.

Patients were randomized per a randomization table generated into 2 groups: Group N (naftopidil group; N = 55) and Group T (tamsulosin group; N = 55). Enrolled patients of both groups were similarly subjected to counseling and work-up comprised of history, focused urological examination, baseline renal function tests (blood urea, serum creatinine), serum PSA, urine analysis/ culture, an ultrasound assessment of prostate kidney, ureter, and bladder (KUB) post-void residue (PVR), and uroflowmetry. Patients in Group N were prescribed naftopidil (50 mg) while Group T patients were prescribed tamsulosin (0.4 mg) daily at bedtime after meals and were followed at 2, 4, 6, and 12 weeks. At each visit, patients were assessed for compliance to therapy, severity of symptoms (by recording the IPSS), and side effects. All patients underwent uroflowmetry and ultrasound examination

literature [3,4]. Another uroselective alpha-blocker (naftopidil) has emerged that blocks α1D-AR and is believed to have a 17-fold higher selectivity for α1D-AR versus α1A-AR, with claims of fewer side effects according to some Japanese studies [5]. Certain published studies [6-8] have shown that naftopidil may

to assess peak flow rate (PFR), average flow rate (AFR), and PVR. Any incidence of AUR and the results of subsequent trials without catheterization (TWOC) were also documented. All interventions were similar in both groups. The basic principle of the clinical intent to treat all symptomatic patients as deemed necessary was firmly adhered to in this study. Tamsulosin and or naftopidil medication(s) were prescribed, and their generic counterparts were not available in our institution at the time of this study. In this study, we endeavored to use only the plain, generic version of both these drugs.

Considering a standard deviation of 7.78 and 6.23 in groups N and T, respectively, for a difference of 4 units in IPSS as significant, 49 cases was required in each group for a power of 80%. Data was recorded in a predesigned proforma and analyzed using appropriate statistical tools such as the unpaired Student t test, Tukey test, and the repeated measure ANOVA test. Compliance to the therapy was assessed by recording the number of patients who failed to take the prescribed medication or who withdrew from the study.

RESULTS

Of the 110 patients, 9 patients defaulted/were lost to follow-up. These were excluded from the analysis, leaving 101 evaluable patients. The salient mean parameters recorded are depicted in Table 1. The mean age, BMI, grade of prostate, average flow rate, IPSS total score, storage subscore IPSS, voiding subscore IPSS, maximum flow rate, post-void residue, quality of life (QoL), SFIS, flow time, hesitancy, voided volume, and prostate volume were comparable in both groups and there was no significant difference noted between the 2 groups (Table 1).

A comparison of changes in chosen parameters between groups N and T after 1 and 3 months of therapy are summarized in Table 2. Four and 5 patients belonging to groups N and T, respectively, developed AUR during therapy; however, the frequency of AUR episodes between the 2 groups was not statistically significant ($P = 1.0$). Of these 9 patients, 7 responded to a trial of micturition without a catheter within 2 weeks while 2 patients were planned for surgical intervention.

The side effects observed in groups N and T are depicted in Table 2 (B). Orthostatic hypotension was initially observed in both groups (not significant) but resolved on follow-up. None of the patients reported asthenia, fatigue, rhinitis, somnolence, impotence, or priapism. All patients were fully compliant to the administered therapy. None of these adverse effects necessitated withdrawal from treatment. Figure 1 and Figure 2 depict a graphical presentation of the change in the salient outcome parameters in patients of symptomatic BPH to the administered therapy over a 3-month period.

Figure 1. a) Trends in IPSS, SFIS, and PVR in patients of symptomatic BPH on naftopidil and tamsulosin therapy over a period of 3 months; b) Change in AFR, QoL, and MFR in patients with symptomatic BPH on naftopidil and tamsulosin therapy over period of 3 months.
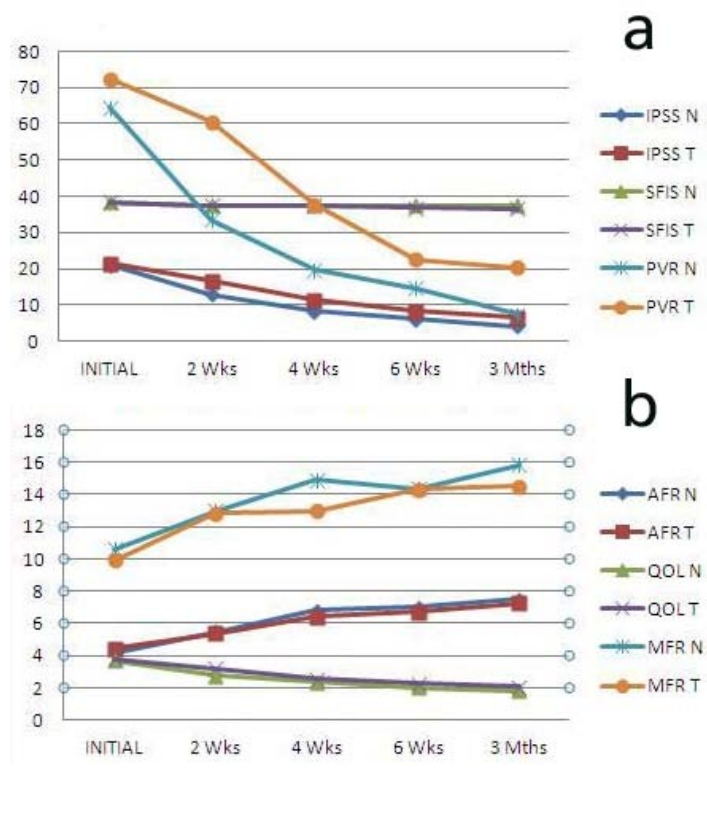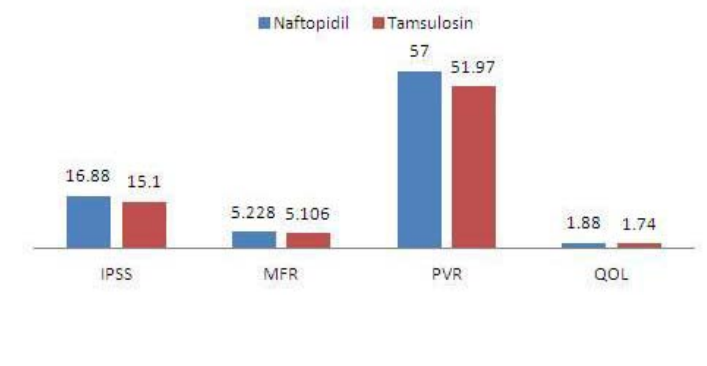

Figure 2. Change in the outcome parameters (from the initial values) in patients with symptomatic BPH on naftopidil and tamsulosin therapy at 2 months.

DISCUSSION

IPSS

Recent comparative Japanese studies [9-11] of naftopidil versus tamsulosin have demonstrated that naftopidil may be superior in efficacy in patients with BPH and predominant storage symptoms, nocturia, low compliance, and overactive bladder. Naftopidil has been well tolerated with some minor side effects that appear to be lower than with tamsulosin therapy [6,7,10]. In our study, both drugs decreased the IPSS score significantly ($P = 0.000$), and the mean change in IPSS was -16.88 and -15.10 for naftopidil and tamsulosin, respectively. In the current study, it appeared that the initial fall in IPSS at 2 weeks of therapy was greater with naftopidil than tamsulosin, which was statistically significant ($P = 0.03$), demonstrating that while both were comparable in decreasing IPSS, as shown in other similar comparative studies [9,10,12-14], the former had an earlier onset of action that may have been due to naftopidil's effect on α1D-receptors in the CNS, bladder, and spinal cord [15,16]. Differences in the α1D-receptor concentration between the Indian and Japanese population may be one of the reasons for greater naftopidil effectiveness in the Indian population compared to the Japanese population. The storage and voiding subscores of IPSS (Table 2) decreased significantly over a period of time, and none were statistically significant after 3 months of therapy. However, we did observe that the storage subscore after 2 weeks of therapy was significantly better with naftopidil ($P = 0.011$). Nevertheless, this data needs to be seen in light of the fact that the power factor for this study was perhaps inadequately powered to achieve validated results. Various studies have also shown that naftopidil may be superior in efficacy in patients with predominant storage symptoms, nocturia, low compliance, and overactive bladder [9-11].

Flow Rates

As depicted in Table 2a, both the drugs were effective in improving the MFR and AFR significantly over a period of time. While an observed change of 5.23 and 5.11 in MFR was noted with naftopidil and tamsulosin, respectively, the same was not statistically significant at any specific interval ($P = 0.349$ for MFR and $P = 0.783$ for AFR). Similar results were seen in the Japanese comparative studies [9,10,12,13].

PVR

There was an appreciable fall in the mean PVR in both groups (see Table 2a), which was comparable to other Japanese studies [9,10,17], but in our study this appeared to be slightly higher with naftopidil after 3 months of therapy, though this difference was statistically significant only at a 2-week interval ($P = 0.041$).

Table 2. a) The change in the outcome parameters of patients in both groups evaluated over 3 months and b) The adverse events recorded in the same patients.

2(a)

Parameter	Drug	Initial	2 Wks	4 Wks	6 Wks	3 Mths
IPSS†	N*	21	12.82	8.38	5.98	4.18
	T*	21.53	16.61	11.41	8.18	6.43
MFR	N*	10.62	12.99	14.91	14.35	15.85
	T*	9.91	12.81	12.99	14.29	14.518
PVR†	N*	64.4	33.42	19.66	14.6	7.4
	T*	72.34	60.59	37.6	22.61	20.37
AFR	N*	4.19	5.49	6.78	7.01	7.48
	T*	4.434	5.36	6.41	6.71	7.26
V-IPSS	N*	10.72	6.56	4.34	3.2	2.26
	T*	10.75	8.18	5.75	3.98	3.06
S-IPSS†	N*	10.46	6.32	4.16	2.78	1.92
	T*	10.49	8.47	6	4.2	3.39
QOL†	N*	3.68	2.74	2.36	2	1.8
	T*	3.78	3.18	2.57	2.27	2.04
SFIS	N	38.27	37.43	37.47	37.4	37.4
	T*	38.42	37.42	37.55	36.9	36.7

N: naftopidil; T: tamsulosin; IPSS: International Prostate Symptom Score out of 35; MFR: maximum flow rate; PVR: post-void residue; AFR: average flow rate; V-IPSS: voiding subscore of IPSS; S-IPSS: storage subscore of IPSS; QoL: quality of life; SFIS: Sexual Function Inventory Score out of 42; *: $P < 0.05$ (significant difference) within the group when initial parameters compared with 3-month parameters; †: $P < 0.05$ (significant difference) between N and T groups at 2-week interval. No parameters were significantly different at 3-month interval.

2(b)

Events	Group N	Group T	P value*
Orthostatic hypotension	8/50 (16%)	12/51 (24%)	0.342
Headache	1/50 (02%)	3/51 (06%)	0.617
Retrograde ejaculation	5/50 (10%)	10/51 (20%)	0.175

*Not Significant

Qol

Regaring Qol, we observed a significant improvement in Qol with both naftopidil and tamsulosin with no overall difference (significantly better at 2 weeks with nafopidil, *P* = 0.017). Various studies [9,10,12-14] show similar results, as found in both our study and another [17] that shows tamsulosin is significantly better than naftopidil in improving Qol.

Side Effects and Withdrawals

As depicted in Table 2b, though the tamsulosin group had more side effects compared to the naftopidil group, there was no statistically significant difference between Group N and Group T in respect to those side effects. None of the patients reported dizziness, asthenia, fatigue, rhinitis, or somnolence during the observed period of this study, and all patients were fully compliant to the administered therapy. According to a Cochrane Database, systemic review of adverse effects due to naftopidil occurred among 34 (15%) participants [18]. The most common adverse effects associated with naftopidil were dizziness and hypotension [18], while 1 study reported numbness of the tongue in some patients taking naftopidil [12]. The most commonly reported adverse effects in a Cochrane review due to tamsulosin were hypotension, dizziness, and headache [18]; furthermore, there were no significant differences in the incidence of adverse events in the control versus treated group [18], which was confirmed by pooled data from 3 other similar trials [12-14]. According to another well-cited study reported by Narayan et al [19], who reviewed the "Long-term efficacy and safety of Tamsulosin for BPH," reported that the most commonly met "treatment-emergent adverse events" were infection, accidental injury, rhinitis, pain, and pharyngitis; and other adverse effects included abnormal ejaculation (8.3%), syncope (1.7%), and postural hypotension (1.3%) [19].

SFIS

In a statistical evaluation of the SFIS, repeatedly measured ANOVA tests and Tukey tests revealed a significant change in SFIS in the tamsulosin group compared to the pretreatment values recorded over our study period (*P* = 0.000; *P* < 0.001). A Tukey test showed the critical difference of 0.930, which was observed in the tamsulosin group starting 2 weeks after starting the drug, thus showing that tamsulosin significantly decreases SFIS within 2 weeks of starting therapy. The naftopidil group had a total difference of -0.870 when comparing the initial value of SFIS to the 1- week value, which was not statistically significant. Another study [20] showed that 0.2 or 0.4 mg of tamsulosin for 3 days resulted in a reduced seminal volume, while 50 or 100 mg of naftopidil for 3 days did not. In another Japanese randomized control study by Masumori et al [17] that investigated the incidence of ejaculatory disorders caused by 50 mg of naftopidil (N = 48) and 0.2 mg of tamsulosin (N = 47)

Table 3. The comparison of the present study with other similar published trials of naftopidl versus tamsulosin for LUTS due to BPH.

Author	Group	Change from Initial				Salient Features of the Study
		IPSS	MFR	PVR	QOL	
Momose et al. (2007) [14]	N	6.7	NR	NR	0.6	RCT; SS-45 (N-20,T-25); 4-wk Rx; No parameter significantly different N vs T
	T	7.3	NR	NR	0.7	
Nishino et al. (2006) [10]	N	11.5	3.8	44.2	2.3	RCT; SS 34 (N-17, T-17);4 wks Rx; no parameter significantly different N vs T
	T	11.1	3.1	43.1	2.2	
Ikemoto et al. (2003) [13]	N to T	8.5	2.1	NR	NR	Crossover RCT; Sample size 96 (N to T-43, T to N-53); 16 weeks (8 x 2, no wash-out period); no parameters were significantly different N vs T
	T to N	9.2	2.1	NR	NR	
Ukimura et al. (2008) [9]	N	9.4	1.3	15.9	2.2	RCT; SS- 59 (N-31,T-28); 6-8-week Rx; N showed a significant early response to improved storage symptoms at 2 wks; no parameters were significantly different N vs T
	T	9.7	2.8	3.5	2	
Gotoh et al. (2005) [12]	N	5.9	2.1	13.6	1.3	RCT; SS-185 (N-69, T-75); 12-week Rx; no parameters were significantly different in N vs T
	T	8.4	2.1	9.6	1.4	
Current Trial	N	16.88	5.228	57	1.88	RCT; SS-101 (N-51,T-50); 12-week Rx; no parameters were significantly different in N vs T at 3 months. At 2 wks, storage symptoms were significantly better in N
	T	15.1	5.106	51.97	1.74	

SS: sample size; RCT: randomized clinical trial; N: naftopidil; T: tamsulosin hydrochloride.

among sexually active men during the 12 weeks, the proportion of patients who reported an abnormal feeling at ejaculation was higher in the tamsulosin group (16.7%) versus the naftopidil group (7.4%); however, they reported that this difference was not significant ($P = 0.402$). Men who reported reduced ejaculatory volume after treatment were significantly higher in the tamsulosin group (96.0%) compared to the naftopidil group (73.1%, $P = 0.0496$), although the improvement of erectile function by α1-blockers has reported [21,22]. No significant change in the International Index of Erectile Function (IIEF)-5 score caused by either drug was observed in this small study. On the other hand, Yokoyama et al [23] showed that the mean IIEF-5 score improved in a naftopidil group (7.0 at baseline to 7.6 at 3 months, $P = 0.013$) but not in the silodosin group (6.2 at baseline to 5.0 at 3 months, $P = 0.682$) or tamsulosin group (6.6 at baseline to 5.2 at 3 months, $P = 0.342$). Thus it appears that naftopidil may be more suitable for relatively younger and sexually active patients. According to a major randomised controlled study [24] with naftopidil, the authors observed that it improved storage and voiding symptoms. In another similar study [25], the authors found naftopidil also benefited patients of BPH with nocturia, improving their quality of sleep though this was not specifically evaluated in the current study.

There were certain limitations in the current study. Due to logistical constraints, the number of patients required for a power of 80 was not initially calculated for this study but was based on similar studies done in the past at our institution. A sample size of 50 in each group was considered while an additional 10 patients were recruited to compensate for 9 patients lost to follow-up. While this study was based on a small sample size wherein the possibility of type II statistical error(s) remains, we admit that a larger study is definitely required to establish the precise role of naftopidil in BPH. There was a no-dose escalation step incorporated in this study protocol for patients not benefitting from 0.4 mg of tamsulosin or 50 mg of naftopidil. According to a review by Masumori et al [26], it is probable that the optimal dosage of naftopidil may vary among individuals based on different α1A/α1D-AR subtype ratios [27]. Furthermore, this was a non-placebo, open-label study, and due to the logistical constraints of a public institution, all patients/physicians were not fully blinded to the administered therapy and the double blinding/allocation concealment in this study was not ideal. Finally, SFIS was evaluable in only 61/101 (60%) patients that were sexually active prior to therapy; therefore, the precise impact of the medication on sexual function could not be evaluated in all our patients.

While it is possible that many of the side effects may partly depend on the applied galenic formulation of the tamsulosin pill, and since we had used only the plain generic version of the tamsulosin pill in this study, it was not feasible for us to evaluate and comment on the difference, if any, in the observed side effects encountered with different galenic formulations of the tamsulosin pill.

CONCLUSION

Naftopidil and tamsulosin were both equally effective in relieving LUTS due to BPH, and patient groups appeared to be equally compliant with either of these drugs. Naftopidil appeared to improve IPSS, the storage subscore of IPSS, PVR, and QoL earlier than with tamsulosin. A higher incidence of postural hypotension and headache were observed in the tamsulosin group compared to the naftopidil group, but this perceived difference was not statistically significant. However, this data should be seen in light of the before-mentioned fact, that in this study the patient numbers needed to be adequately powered to achieve more consistent observations and validated results. Sexual function inventory score was significantly lower in the tamsulosin group while naftopidil group did not show a significant reduction in the SFIS score. While the prospect of apparently lower sexual dysfunction observed with naftopidil appears to be attractive, further comparative trials for evaluation of the same appear to be obligatory, and as mentioned before, this data again needs to be seen in light of the fact that sexual side effect(s) that appeared to be reduced in this study could not be decisively addressed due to several patients not providing data.

Patients of both naftopidil and tamsulosin groups were equally compliant, and there was no treatment withdrawal from our study on account of the side effects of the drugs being administered. Finally, prospective, large-scale, randomized clinical studies of naftopidil with tamsulosin for BPH as a whole with ample statistical power to draw authentic conclusions are needed.

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