

EFFECT OF A COMBINATION OF DUTASTERIDE AND PARENTERAL TESTOSTERONE UNDECANOATE ON TESTOSTERONE DEFICIENCY SYMPTOMS AND PROSTATE IN PATIENTS WITH TESTOSTERONE DEFICIENCY AND BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Background and objective

The effect of a combination of testosterone and 5-Alpha reductase inhibitors (5-ARIs) on serum testosterone levels, TD symptoms, and the prostate are not sufficiently established. Therefore, we examined the effects of long-acting parenteral testosterone undecanoate (TU) and dutasteride used in combination for the treatment of BPH patients with TD.

Subjects and methods

We selected 130 patients with a prostate volume (PV) > 30 g from those diagnosed with TD and had received parenteral TU for 1 year. These patients were assigned to the following two groups: Group I, which comprised patients who received TU injections along with dutasteride, and Group II, which included patients with TU-only treatment. Statistical analyses were performed between the two groups to compare the results of serological tests, symptom questionnaire scores, and PV.

Results

No significant differences were observed in the baseline characteristics such as mean age, comorbidities, testosterone levels, symptom questionnaire scores between the two groups. There were no significant differences in the testosterone levels or the change in testosterone levels after treatment between the two groups. The PV was significantly increased in Group II and significantly decreased in Group I. Both groups showed a significant increase in the total scores and all subscale scores of the IIEF and AMS after treatment. Group II had a significantly higher total IIEF score than Group I and a significantly lower score in the sexual function subscale of the AMS after treatment.

Conclusions

The combination of TU and dutasteride considerably improved serum testosterone levels, alleviated TD symptoms, and effectively reduced PV in patients with TD and BPH. However, compared with the TU-only treatment, the combination was less effective in improving symptoms related to sexual function. Therefore, dutasteride should be used with caution when treating BPH patients with TD, who mainly complain of sexual dysfunction.

Key Words: *benign prostatic hyperplasia; dihydrotestosterone; dutasteride; testosterone deficiency; testosterone undecanoate*

INTRODUCTION

Parenteral testosterone undecanoate (TU; 1000 mg) has been proven to be an effective and safe medication for Korean patients with testosterone deficiency (TD).¹ 5-Alpha reductase inhibitors (5-ARIs) are used to treat benign prostatic hyperplasia (BPH) and are effective in reducing the levels of dihydrotestosterone (DHT) in the prostate and thereby prevent its growth. Depending on which of the two types of 5-alpha reductase (type 1 or 2) is to be inhibited, two 5-ARIs, finasteride and dutasteride, are clinically used.²⁻⁴ There are some controversies, but some studies have reported that dutasteride exhibits more sexual adverse effects such as erectile dysfunction (ED), ejaculatory dysfunction, and decreased libido than finasteride.^{5,6}

Several studies have reported the effects of testosterone treatment (TRT) on the prostate, including an increase in prostate volume and prostate-specific antigen (PSA) levels during the first 6–12 months of treatment.⁷ However, conflicting results have also been reported regarding the efficacy of TRT in terms of reducing prostate volume and relieving lower urinary tract

symptoms (LUTS).^{8,9} Although TRT and 5-ARIs are frequently used in combination for BPH patients with TD, studies on the effect of TRT on the efficacy of dutasteride against BPH are limited. Moreover, the effects of a combination of long-acting injectable TU and dutasteride on the prostate have yet to be investigated.

5-ARIs reduce the levels of DHT in the prostate and blood, and several studies have reported that 5-ARI treatment may lead to a significant increase in the total testosterone (TT) levels in the serum, particularly in men with low baseline TT levels.^{10,11} Even at increased TT levels, dutasteride, which inhibits both type 1 and type 2 alpha reductases, has been reported to increase the risk of sexual dysfunction, including decreased libido and semen volume, and ED.¹² To date, there has also been limited research on the effect of a combination of TRT and 5-ARIs on serum TT levels and TD symptoms. Furthermore, there have been no studies that have examined the effects of a combination of long-acting injectable TU and dutasteride.

Given the limited data currently available, in this study, we aimed to investigate the effects of a

combination therapy with long-acting injectable TU and dutasteride on prostate volume, serum TT levels, and TD symptoms.

MATERIALS AND METHODS

We primarily investigated 130 patients with a prostate volume >30 g among those who had received injections of long-acting TU (1000 mg) for 1 year after being diagnosed with TD at two medical institutions from 2012 to 2017. Their medical records were retrospectively examined to select patients who were taking dutasteride in combination with TU for 1 year (Group I, n=22) and those who received TU injections without dutasteride or finasteride for 1 year (Group II, n=38). Patients were clinically diagnosed with TD if they had one or more of the symptoms of TD and a serum TT level of <350 ng/dL. TRT was performed only if it was not contraindicated in the guidelines.¹³ Patients who received another TRT within 3 months prior to the TU treatment, those who received 5-ARI within 6 months prior to the TU treatment, or those who switched to or added phosphodiesterase-5 inhibitors during the TU treatment were excluded. In addition, patients who had a medical condition that could affect testosterone levels or cause changes in the prostate during TU treatment (e.g., steroid use, long-term hospitalization or surgery, diabetes mellitus, thyroid disease, brain disease, surgery for BPH, and prostate biopsy) were also excluded. Patients were included only if their records of serum TT, PSA levels, self-assessment questionnaire [International Index of Erectile Function (IIEF) and Aging Males Symptoms Scale (AMS)] scores, and prostate volume measured by transrectal ultrasounds were available. The patients' age, underlying diseases, and medical history were investigated.

To assess changes in the parameters during the pre- and post-treatment periods, and to enable comparisons between the groups, statistical analyses

were performed using the paired t-test, independent t-test, or chi-square test. The results were considered statistically significant if the p-value was <0.05.

RESULTS

The mean age of patients and their underlying diseases were not significantly different between the two groups (Table 1). There were no significant differences between the two groups with respect to the proportions taking alpha blockers or phosphodiesterase-5 inhibitors and their different types, which could affect sexual function. Furthermore, although there were no significant differences in the serum TT, PSA, or IIEF and AMS scores prior to TU treatments in the two groups, the baseline prostate volume was significantly higher in Group I than in Group II (Table 1).

Both groups showed a significant increase in serum TT levels following treatment, whereas no significant differences in serum TT levels were observed between the two groups after treatment (Table 2). Although we detected a higher increase in serum TT levels following treatment in Group I patients compared with those in Group II, the increase was not statistically significant (p=0.814). Furthermore, there was a statistically significant reduction in the prostate volume of Group I patients from 41.2 to 33.5 g, whereas a significant increase in the prostate volume from 32.8 to 36.0 g was observed in Group II patients (Table 2). Statistically significant improvements in the IIEF and AMS scores were observed in both groups following treatment. Although no significant differences were observed in the IIEF orgasmic function or sexual desire subscale scores between the two groups, other subscale and total IIEF scores were significantly higher in Group II than in Group I. No significant differences were observed in the AMS psychogenic and somatic subscale scores between the two groups, whereas Group II showed a significantly better symptom score in the sexual subscale of AMS (Table 2).

TABLE 1 Comparison of the baseline characteristics between the two patient groups (Group I: parenteral testosterone undecanoate+dutasteride, and Group II: parenteral testosterone undecanoate only)

	Group I (n=22)	Group II (n=38)	p-value*
Age	61.72 ± 3.15	59.22 ± 7.31	0.133
Total testosterone (ng/dL)	280.58 ± 64.54	288.13 ± 65.76	0.695
PSA (ng/mL)	1.31 ± 0.92	1.19 ± 0.71	0.062
Prostate volume (g)	41.19 ± 10.80	32.80 ± 3.68	0.004
Comorbidities, N			0.508
None	4/22	9/38	
Hypertension	7/22	10/38	
Diabetes mellitus	4/22	7/38	
Dyslipidemia	7/22	12/38	
Hepatobiliary disease	2/22	4/38	
Pulmonary disease	2/22	3/38	
IIEF total	33.67 ± 3.74	33.37 ± 9.61	0.908
Erectile function	12.13 ± 2.47	13.56 ± 3.55	0.175
Orgasmic function	4.70 ± 2.90	4.66 ± 2.04	0.950
Sexual desire	4.47 ± 1.73	4.76 ± 2.36	0.674
Intercourse satisfaction	4.12 ± 2.90	4.01 ± 2.03	0.618
Overall satisfaction	3.53 ± 1.96	4.82 ± 2.28	0.071
AMS total	37.35 ± 8.65	35.70 ± 12.64	0.645
Psychogenic	8.35 ± 1.84	9.74 ± 3.51	0.146
Somatic	14.12 ± 4.40	13.87 ± 5.29	0.876
Sexual	14.76 ± 3.33	13.09 ± 4.71	0.214

IIEF, International Index of Erectile Function; AMS, Aging Males' Symptoms Scale.

*Independent t-test or chi-square test.

DISCUSSION

In this study, we address concerns regarding the inhibition of the effect of dutasteride, which limits prostate growth by reducing the DHT levels, by TRT, and succeeded in resolving this problem to some extent. The combination of TU and dutasteride reduced prostate volume and PSA levels considerably after 1 year of treatment. This is in marked contrast to the increase in prostate size and PSA levels observed in the TU-only group. The increase in prostate volume and PSA levels in the TU-only group is assumed to be attributable to the influence of exogenous

testosterone on prostate growth until it reaches the eugonadal state. In this regard, a long-term follow-up of patients may confirm the saturation theory of Morgentaler et al.¹⁴ Recent TD guidelines no longer mention BPH or LUTS as contraindications for the treatment of TD.¹⁵⁻¹⁷

In this study, we observed significant differences in the IIEF scores and AMS sexual subscale scores between the two patient groups. The differences in these scores may be due to a reduction in DHT levels induced by dutasteride. Roehrborn et al.¹⁰ and Hong et al.¹¹ evaluated the effect of finasteride and dutasteride on TT and reported

TABLE 2 Comparison of the two patient groups after 1 year of treatment (Group I: parenteral testosterone undecanoate+dutasteride, and Group II: parenteral testosterone undecanoate only)

	Group I (n=22)	Group II (n=38)	p-value [‡]
Total testosterone (ng/dL)	475.90 ± 209.75**	470.25 ± 227.67**	0.924
PSA (ng/mL)	0.80 ± 0.81*	1.19 ± 0.60	0.938
Prostate volume (g)	33.54 ± 8.92**	36.01 ± 5.60*	0.284
IIEF total	50.75 ± 9.01**	59.79 ± 8.81**	0.003
Erectile function	18.81 ± 5.04*	24.21 ± 5.31**	0.002
Orgasmic function	8.56 ± 2.00*	8.59 ± 1.68**	0.966
Sexual desire	6.75 ± 1.69*	7.07 ± 1.56**	0.527
Intercourse satisfaction	10.31 ± 2.47*	12.24 ± 1.94**	0.006
Overall satisfaction	6.19 ± 1.28*	7.69 ± 1.23**	0.001
AMS total	31.25 ± 8.11*	26.71 ± 5.61*	0.063
Psychogenic	7.75 ± 2.79*	6.54 ± 1.50*	0.128
Somatic	12.31 ± 4.19*	11.33 ± 3.29*	0.414
Sexual	10.81 ± 3.41*	8.83 ± 2.37**	0.036

IIEF, International Index of Erectile Function; AMS, Aging Males' Symptoms Scale.

* $p < 0.05$, ** $p < 0.01$; paired *t*-test compared to baseline in each group.

[‡]Independent *t*-test between two groups.

that TT levels generally increased following 5-ARI administration. In this study, we observed a greater, although statistically non-significant, change in TT levels in the TU+dutasteride group compared with that in the TU-only group. Despite an increase in serum TT levels, 5-ARIs often cause sexual dysfunction, such as erectile dysfunction (ED) and reduced libido, as complications that are related to a decrease in the levels of DHT.^{4,18} A reduction in DHT can lead to reduced levels of nitric oxide and nitric oxide synthase in the corpus cavernosum, which subsequently affects erectile function, given that DHT induces a stronger expression of nitric oxide synthase in the penile corpus cavernosum than does testosterone.¹⁹ In addition, sexual desire and orgasm are considered to be promoted via sex hormone receptors in the hypothalamus or amygdala in the brain. It is known that these receptors are located in neurons and glial cells, in which 5- α reductase is expressed. 5-ARIs, such as finasteride, can

pass through the blood–brain barrier to inhibit DHT production within the central nervous system,^{20,21} and therefore, reduced libido following 5-ARI administration may be closely associated with a reduction in DHT levels. Accordingly, BPH treatment should be administered with care in patients with TD who report sexual dysfunction, such as ED or reduced libido, as primary symptoms, as dutasteride can reduce the positive effects of TU on sexual function.

In this study, we found that patients in the TU+dutasteride group had a higher score in the sexual subscale of AMS than did those in the TU-only group. However, no significant differences in scores were observed between the two groups with respect to the other subscales of AMS. In the study conducted by Page et al.,²² the authors found that the addition of finasteride to TRT did not significantly alter the positive effects of testosterone on physical performance, grip strength, or lean body volume, thereby indicating that normal

DHT levels are not essential for testosterone to exert its anabolic effects on muscles. This finding is consistent with the findings of the present study in that we observed that there was no significant difference between the two groups with respect to scores in the somatic subscale of AMS.

Both TD and BPH are commonly observed to co-occur in clinical settings. The use of dutasteride in conjunction with TRT for the treatment of BPH is also not uncommon. However, only a few studies have been conducted to examine the effects of the combination of TRT and dutasteride on the prostate and TD symptoms, and the results have been inconsistent and limited. In their placebo-controlled trial, Bhasin et al. assigned subjects to four groups and administered different doses of testosterone enanthate (TE) injection together with 2.5 mg of dutasteride. After 20 weeks of treatment, they compared TT levels, body composition, muscle strength, IIEF, and Male Sexual Health Questionnaire scores with the corresponding parameters in subjects in the TE injection with placebo group.²³ However, the study had a clinically impractical design, as the enrolled subjects were healthy men aged 18–50 years with normal testosterone levels (300–1200 ng/dL) and were randomized after testosterone suppression using leuprolide acetate. Given that the subjects were healthy males without BPH, as opposed to patients who would typically be clinically diagnosed with TD, only half of the standard dose (0.25 mg) of dutasteride was used. Bhasin et al. concluded that the conversion of testosterone to DHT is not essential for mediating the anabolic effects of testosterone on muscles, based on the fact that they did not observe any significant difference in fat-free volume, muscle strength, TT, prostate volume, or PSA between the two groups, even after DHT suppression by dutasteride. However, considering the unrealistic research design, their findings do not directly address the issue regarding the effect of dutasteride on testosterone and TD symptoms. In a double-blind,

placebo-controlled trial conducted by Page et al.,²⁴ 53 patients, with symptomatic BPH, reduced serum TT levels of 280 ng/dL, and a prostate size >30 g, were subjected to a 6-month combination therapy using 1% testosterone gel together with dutasteride and compared with patients in a testosterone gel plus placebo group. The patients in the placebo group showed an increase in prostate volume and PSA level following the treatment, whereas those in the dutasteride group showed a significant reduction in prostate size and PSA level, suggesting that dutasteride protects the prostate from testosterone stimulation. However, the study included patients with symptomatic BPH and reduced TT levels regardless of whether they had TD symptoms. Moreover, the treatment period was short (6 months), and TD symptoms and erectile function were not evaluated.

In most studies that have evaluated the combination of testosterone and 5-ARIs, oral TU,²² testosterone gel,²⁴ and TE injections²³ have been used. There are, however, certain problems associated with the use of these forms of medication, as they should ideally be frequently applied or injected owing to their short duration of action. Thus, in the present study, we only included those patients who had been treated with a long-acting injectable TU, which has a longer duration of action and maintains serum TT levels within the physiological range. We selected parenteral TU on the basis that it has been proven to be safe and effective in the Korean population by Moon et al.,¹ and it also achieves a higher compliance than the other forms of testosterone.

To the best of our knowledge, this study is the first to investigate the effects of combination therapy based on long-acting injectable TU and dutasteride for treatment of the prostate and TD symptoms. However, in addition to its retrospective design, the study does have certain other limitations. First, owing to the small sample size of patients, the statistical analyses conducted in this study have insufficient statistical power. Furthermore, we did

not examine those factors related to metabolic syndrome that may be associated with TD and BPH. It is also possible that information was missing regarding those patients who discontinued treatment due to either unsatisfactory efficacy or adverse effects, which, accordingly, may have biased our analysis. Moreover, the study relied on self-assessment questionnaires rather than objective evaluation tools, such as the penile Doppler test, to evaluate the erectile function in patients. Finally, owing to a lack of International Prostate Symptom Score (IPSS) and uroflowmetry results, we did not evaluate LUTS, which might be associated with BPH.

CONCLUSIONS

The combination of TU injection and dutasteride considerably improved serum testosterone levels and TD symptoms and effectively reduced prostate size in patients with TD and BPH. However, the combination was less effective than the TU-only treatment in improving erectile function and TD symptoms related to sexual dysfunction. Dutasteride should be used with care when treating BPH patients with TD, who primarily complain of sexual dysfunction, because there is a possibility that reduced levels of DHT may affect sexual function in these patients. Further, large-scale prospective studies are needed to confirm these findings.

CONFLICT OF INTEREST

We have no conflict of interest to declare.

FUNDING

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