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Efficiency of intracavernosal alprostadil and oral clomiphene citrate combination treatment in penile vasculogenic erectile dysfunction patients accompanied by late-onset hypogonadism

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Abstract

In this study, the efficiency of intracavernosal alprostadil + oral clomiphene citrate (CC) treatment in late-onset hypogonadism (LOH) accompanied by penile vasculogenic erectile dysfunction (PVED) in patients irresponsive to phosphodiesterase type 5 inhibitor treatment was evaluated. A total of 31 patients with concurrent PVED and LOH were included in the study. The patients were given intracavernosal alprostadil (10–20 μg) and oral CC (50 mg) every day for 12 weeks. Before and after treatment, a 15-question International Index of Erectile Function (IIEF-15) questionnaire, Erection Hardness Score (EHS), Sexual Encounter Profile (SEP)2 and SEP3 levels were analysed, and follicle stimulating hormone (FSH), luteinising hormone (LH), total testosterone and prostate-specific antigen (PSA) levels were measured. In all, 41.9% of patients had pure arterial deficiency, 19.3% had pure venous deficiency, and 38.7% had arterial + venous (mixed) deficiency. A significant increase was detected in total testosterone, FSH, LH and PSA values after treatment when compared to values before treatment ($p < .001$, $p < .001$, $p < .001$ and $p = .034$ respectively). A significant recovery was observed in IIEF-15 subscores, EHS and SEP2-SEP3 results. In PVED patients accompanied by LOH, intracavernosal alprostadil and oral CC combination is an efficient, low cost, safely applicable and tolerable treatment.

KEYWORDS

alprostadil, clomiphene citrate, erectile dysfunction, hypogonadism, intracavernosal treatment

1 | INTRODUCTION

Erectile dysfunction (ED) refers to difficulty in starting and maintaining an adequate erection for satisfactory sexual performance and the stability of this condition (Burnett et al., 2018). The estimated prevalence of ED in men > 40 years of age is almost 50% (Bella, Lee, Carrier, Benard, & Brock, 2015). Different therapeutic agents have been developed for ED treatment, and their effect mechanism depends on the understanding of erection physiology. In ED treatment-resistant patients, lifestyle changes as a first-line treatment option and phosphodiesterase type 5 inhibitors (PDE5 inhibitors) as a second-line treatment option are used. PDE-5 inhibitors are noninvasive, generally well tolerated and efficient in most males. Intracavernosal injections (ICUs), such as alprostadil and papaverine, can be used in 25%–50% of patients who are irresponsive to the treatment and who contraindicate PDE5 inhibitors (Bella et al., 2015; Hatzimouratidis et al., 2019).

The International Society of Andrology (ISA), International Society for the Study of the Aging Male and the European Association of

Urology defined late-onset hypogonadism (LOH) as a clinical and biochemical syndrome forming as the result of ageing in males (Nieschlag et al., 2006). Symptoms and impaired quality of life can be observed due to multiple organs being affected in the clinical stage of this syndrome, which demonstrates itself biochemically in decreasing serum testosterone levels (Nieschlag et al., 2005). It has been shown that total testosterone biochemically decreases by an annual rate of 0.8% and bioactive testosterone decreases by an annual rate of 1.6% in males after the age of 40. The cause of the lower decrease in total testosterone compared to bioactive or free testosterone is considered to be the increase in sex hormone-binding globulin with ageing. Hypogonadism prevalence was reported as ranging at 2%–30% between the ages of 40 and 59 and as 20%–45% between the ages of 60 and 69 and gradually increases with age (Huhtaniemi, 2014; Nieschlag et al., 2005; Üçer & Gümüş, 2014). Provision of a treatment to replace missing testosterone is suggested in symptomatic individuals with a total testosterone level below 346 ng/dl (12 nM) (Kim & Moon, 2011; Wang et al., 2009).

There are many studies showing that clomiphene citrate (CC) can be used as an alternative to testosterone treatment. Clomiphene citrate increases testosterone production in the testicles through hypothalamo-pituitary feedback inhibition. Clomiphene most likely does not have any negative effect on spermatogenesis. Additionally, CC application is an advantageous method in terms of treatment cost (Guay, Bansal, & Heatley, 1995; Taylor & Levine, 2010).

In ED, the combination of pharmacotherapeutical treatments may have a positive and synergic effect for improving erectile function since these agents can treat patients by targeting different points in the erection physiological pathway (Duncan et al., 2019). In this study, the efficiency of intracavernosal alprostadil and oral CC combination treatment in LOH accompanied by penile vasculogenic ED (PVED) patients irresponsive to PDE inhibitor treatment is evaluated.

2 | MATERIAL AND METHODS

2.1 | Patient evaluation

The article is in accordance with ethical standards and was approved by the local ethics committee (approval number: NEU-20202494).

Patients referred to the andrology clinic in a university hospital with complaint of ED between January 2016 and September 2019 were evaluated. Presence of cardiovascular disease, hypertension (HT) and diabetes mellitus (DM), which are vascular comorbidities, was questioned, and details related to it were recorded.

A careful and detailed anamnesis was taken in order to eliminate psychogenic and neurological factors, and a general neurological examination and genital examination, especially evaluation of secondary sex characteristics, were performed.

Depending on patient medical history, sexual function and ED degree were determined using the 15-question International Index of Erectile Function (IIEF-15) questionnaire, Erection Hardness Score (EHS), Sexual Encounter Profile (SEP) 2 (Were you able to insert your penis into your partner's vagina?) and SEP 3 (Did your erection last long enough for you to have successful intercourse?) before and after treatment.

Hormonal laboratory values (follicle stimulating hormone [FSH], luteinising hormone [LH], total testosterone and prostate-specific antigen [PSA]) were examined. Blood samples were drawn from the antecubital vein at 08:00–10:00 a.m. after an overnight fasting period. These samples were taken twice, before and after treatment on different days. The blood samples were collected in tubes containing dipotassium ethylenediaminetetraacetic acid. All of the measurements were performed immediately after venipuncture to prevent in vitro platelet activation.

Penile Doppler ultrasonography (PDU) was taken in patients suspected to have vasculogenic ED. After the operation, 60 mg papaverine Hc1 was applied by intracavernosal injection from the 1/3 zone of the penis proximally with a 26-gauge and 2-ml injector. Then, in the fifth, tenth, fifteenth and twentieth minutes, arterial and venous penis flows were evaluated. Measurements were made with Siemens Acuson S2000, 9 Mhz linear probe. Arterial deficiency (arteriogenic ED) was diagnosed in patients with a pansystolic blood flow velocity (PSV) under 30 cm/s, venous insufficiency (venogenic ED) in patients with end-diastolic flow velocity (EDV) above 3 cm/s, and mixed ED in patients with both. According to PDU results, patients with penile vasculogenic deficiency (arteriogenic + venogenic + mixed) were considered as having PVED (Sikka, Hellstrom, Brock, & Morales, 2013).

2.2 | Treatment protocol

Alprostadil (Jectera®, Vem Pharmaceuticals) application was administered using a 0.5-inch and 27- to 30-gauge needle. Visible veins were avoided by injecting in the dorsolateral direction of the proximal third of the penis. Starting dose was 10 mcg in all patients. The first injection was made by the health staff, and the patient was trained for its application at home before sexual intercourse. Patients applied the drugs themselves at home after the starting dose. The alprostadil dose was increased to 20 μg in patients who could not provide sufficient erection for vaginal penetration with 10 μg. Oral CC 50 mg (Klomen®, Koçak Farma Pharmaceuticals And Chemical Industry Inc.) was used daily for testosterone replacement. Intracavernosal alprostadil and oral CC combination treatment was used for 12 weeks.

2.2.1 | Inclusion criteria

According to the anamnesis, patients with complaints that were present for more than 12 weeks, aged over 40, and without psychogenic and neurological disease story were included in the study.

Furthermore, based on laboratory parameters, patients whose total testosterone level was below 346 ng/dl (12 nM) (Wang et al., 2009) and who had normal or low PSA (0–3.5 ng/dl), FSH (<11.95 mIU/mL) and LH (<8.6 mIU/mL) values qualified for participation in the study.

In terms of PDU results, patients diagnosed with PVED whose peak systolic velocity (PSV) was <30 cm/s and/or end-diastolic velocity (EDV) > 3 cm/s) (Sikka et al., 2013) were included in the study.

Lastly, according to the treatment, patients who had no medical treatment other than PDE5 inhibitors and who had no treatment history other than intracavernosal and intraurethral treatment, who had used PDE5 inhibitors for at least 12 weeks without benefiting from the treatment, who had received only CC treatment as testosterone replacement and who were able to receive intracavernosal alprostadil + oral clomiphene treatment for at least 12 weeks were included in the study.

2.2.2 | Exclusion criteria

According to the anamnesis, patients whose complaints were present for less than 12 weeks, who were under 40 years of age, and who had a history of psychogenic and neurological disease, malignancy or who had pelvic or penile surgery were excluded.

Furthermore, based on laboratory parameters, patients whose total testosterone was >346 ng/dl (12 nM) (Wang et al., 2009), whose PSA was > 3.5 ng/ml, whose FSH was > 11.95 mIU/mL and whose LH was > 8.6 mIU/mL were also unqualified.

According to PDU, patients with results at normal ranges (PSV > 30 cm/s and/or EDV < 3 cm/s) (Sikka et al., 2013) were also excluded from participation.

Lastly, based on treatment, patients who had a history of intracavernosal and intraurethral treatment, who did not use PDE 5 inhibitors earlier or who used it for a period less than 3 months, and who used testosterone medication other than CC for testosterone replacement treatment were excluded from the study.

Among the 53 patients using CC + alprostadil combination, 22 patients were excluded according to exclusion criteria (seven, due to anamnesis-related factors; five, due to laboratory parameters; two, due to PDU results; eight, due to treatment-related factors).

A total of 31 patients meeting the criteria were included in the study, and the erection function scores and hormonal parameters of the patients were measured before and after treatment and compared.

2.3 | Statistical analysis

Statistical analysis was performed with SPSS, v.23.0 statistical software (SPSS, Inc.). Quantitative data were presented as mean ± standard deviation (*SD*). Normal distribution and differences between variances were determined using Kolmogorov–Smirnov and Levene tests respectively. The McNemar test and Wilcoxon signed-rank test were used to analyse the relationship between categorical and quantitative variables before and after treatment. Kruskal–Wallis and chi-square (χ^2) tests were used to compare the relationship between categorical and quantitative variables PVED subgroups. Lastly, a p value below .05 was considered statistically significant.

3 | RESULTS

A total of 31 patients taking alprostadil and CC combination treatment were included in the study. The mean age of the patients was 54.13 ± 11.6 years. Furthermore, 58.1% (18/31) of the patients had DM, 48.3% (15/31) had HT, and 22.6% (7/31) had coronary artery disease. A PSV of 21.8 ± 8.1 cm/s and an EDV of 5.12 ± 4.5 cm/s were the mean values measured based on PDU results. In all, 41.9% (13/31) of the patients had pure arterial deficiency, 19.3% (6/31) had pure venous deficiency, and 38.7% (12/31) had arterial + venous (mixed) deficiency. A significant increase was detected in total testosterone, FSH, LH and PSA values after treatment when compared to the values before treatment ($p < .001$, $p < .001$, $p < .001$ and $p = .034$ respectively). Details on pre- and post-treatment hormonal parameters are presented in Table 1. A significant recovery was also observed in erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction scores, EHS Score, and SEP2 and SEP3 results (which are IIEF-15 sub-unit scores evaluating pre and post-treatment sexual function). Parameters evaluating sexual function are illustrated in Table 2.

The patient population was divided into three groups based on penile vascular insufficiency: arterial, venous and mixed. Among these groups, a significant difference was detected only between post-treatment Intercourse Satisfaction Score (IIEF-15) and post-treatment total testosterone levels among hormonal and sexual parameters, and both of these parameters had the best values in the arterial deficiency group and worst values in the venous deficiency groups ($p = .009$ and $p = .013$ respectively) (Table 3). A significant difference was not detected among other pre- and post-treatment hormonal and sexual parameters (all parameters $p > .05$).

Following the 12-week treatment phase, two patients (6.4%) reported that they could not continue alprostadil treatment due

TABLE 1 Pre-treatment and post-treatment hormonal parameters

Parameters	Pre-Treatment	Post-Treatment	*p* Value[a]
Total testosterone (ng/dl) mean ± *SD*	280.7 ± 63.9	502.13 ± 175.5	<.001
FSH (mIU/mL) mean ± *SD*	5.16 ± 2.4	8.77 ± 7.7	<.001
LH (mIU/mL) mean ± *SD*	4.65 ± 2.1	6.95 ± 2.83	<.001
PSA (ng/dl) mean ± *SD*	1.68 ± 0.89	1.77 ± 0.89	.034

Abbreviations: FSH, follicle stimulating hormone; LH, luteinising hormone; PSA, prostate-specific antigen.

[a]Wilcoxon's signed-rank test.

TABLE 2 Details of sexual parameters before and after treatment

Parameters	Pre-treatment	Post-treatment	*p* Value
Erectile Function Score (IIEF-15)	9.03 ± 5.33	20.1 ± 5.99	<.001[a]
Orgasmic Function Score (IIEF-15)	3.13 ± 2.5	7.5 ± 2.4	<.001[a]
Sexual Desire Score (IIEF-15)	3.83 ± 1.48	8.19 ± 1.4	<.001[a]
Intercourse Satisfaction Score (IIEF-15)	3.58 ± 2.7	8.94 ± 2.64	<.001[a]
Overall Satisfaction Score (IIEF-15)	4 ± 1.65	8.16 ± 1.55	<.001[a]
EHS	1.13 ± 0.7	2.65 ± 0.8	<.001[a]
SEP 2 *n* (%)			
No	24 (77.4)	4 (12.9)	<.001[b]
Yes	7 (22.6)	27 (87.1)	
SEP 3 *n* (%)			
No	28 (90.7)	11 (35.5)	<.001[b]
Yes	3 (9.7)	20 (64.5)	

Abbreviations: EHS, Erection Hardness Score; IIEF-15, 15-question International Index of Erectile Function questionnaire; SEP, Sexual Encounter Profile.

[a]Wilcoxon's signed-rank test.

[b]McNemar's test.

to penile pain. Priapism was observed in two patients (6.4%) in the treatment phase.

4 | DISCUSSION

Erectile dysfunction prevalence increases with age. While the prevalence changes between 1% and 10% globally in males under 40 years of age, it increases to 15% for males between 40 and 49, 30% for those between 50 and 59, 40% for those between 60 and 69, and 50%–100% for males between 70 and 90 years of age (Lewis et al., 2010).

ED pathology can be vasculogenic, neurogenic, anatomic, drug-related and/or psychogenic. Vasculogenic ED among these forms is the most common among the organic causes of ED (Yafi, Jenkins, & Albersen, 2016). Vasculogenic ED starts due to vessel wall destruction and decreasing vascular elasticity caused by factors, such as high blood pressure, diabetes, dyslipidemia and smoking. Hypoxia caused by decreased cavernosal oxygenisation may normally cause a decrease in prostaglandin E1 levels, inhibiting pro-fibrotic cytokines, such as transforming growth factor β1. As shown in different rat models, these pro-fibrotic cytokines increase collagen accumulation replacing the smooth muscle and cause a decrease in penis elasticity (Moreland, 1998). As the smooth muscle/collagen ratio decreases and collagen content increases, the ability of corpus cavernosum to compress subtunical veins decreases and veno-occlusive dysfunction forms (Nehra et al., 1996).

In the PDU following intracavernosal vasoactive agent injection in the patient examined for ED, peak systolic blood flow rate over 30 cm/s in both cavernosal arteries shows normal arterial system, whereas end-diastolic blood flow rate below 3 cm/s demonstrates the presence of normal venous function. Vascular ED should be considered in the presence of abnormal findings (Sikka et al., 2013). It was measured as a PSV of 21.8 ± 8.1 cm/s and EDV of 5.12 ± 4.5 cm/s with PDU in the patients in our study. Furthermore, 41.9% (13/31) of the patients had pure arterial deficiency, 19.3% (6/31) had pure venous deficiency, and 38.7% (12/31) had arterial + venous (mixed) deficiency. Intracavernosal injection treatments can be used in patients not benefiting enough from first-line treatment modalities in ED treatment, in patients who have contraindicated conditions for PDE5i use and for those who do not prefer to take oral drugs. Alprostadil, papaverine and phentolamine are agents which can be used for this aim (Duncan et al., 2019).

Papaverine is a nonselective PDE-5 inhibitor, which causes the relaxation of smooth muscle by increasing intracellular cAMP and decreasing intracellular calcium concentrations and which provides erection. Papaverine has not been approved for monotherapy as it has severe side effects, such as priapism (6%–7%) and penile fibrosis (5.7%–11%), and is used in combination treatments (Hatzimouratidis et al., 2016). Thus, we preferred not to use papaverine with our patients. Alprostadil is a synthetic form of prostaglandin E1 which is bound to certain receptors on flat muscle cells and which increases cAMP by activating intracellular adenylate cyclase, and it also provides flat muscle relaxation. It is the only intracavernosal treatment agent approved for used in ED treatment by the FDA. It provides complete erection in 70%–80% of ED patients at doses ranging between 10 and 20 μg (Buvat et al., 1998; Khera & Goldstein, 2011).

The most common side effects of the treatment are pain in injection location or during erection (11%), haematoma/ecchymosis (1.5%), long-term erection/priapism (1%–5%) and penile fibrotic lesions (2%) (Linet & Ogrinc, 1996). Advantages of alprostadil compared to other intracavernosally applied agents include lengthened erection and lower systemic side effects and penile fibrosis incidence. For our patients not benefiting from first-line treatment in our study, we recommended alprostadil treatment as it is the only intracavernosal injection agent approved by the FDA, and it has a low side effect profile and high efficiency. We acquired a statistically significant response in all sexual function parameters in all patients at the end of the 12-week treatment. Penile pain and priapism were the most common side effects in our patients, and it occurred at a rate of 6.4%. The monthly treatment cost was approximately $26.

Hypogonadism is a condition which should be carefully examined among the causes of ED. Testosterone level decreases with age in males. Low testosterone rates were detected at 19%, 28% and 49% in 60-, 70- and 80-year-old males, respectively, in a Baltimore longitudinal study on ageing (Harman, Metter, Tobin, Pearson, & Blackman, 2001). Several organisations have defined

TABLE 3 Significantly changing parameters of penile vascular erectile dysfunction subgroups after treatment

Parameters	Arteriogenic ED group ($n = 13$)	Venogenic ED group ($n = 6$)	Mixed Vasculogenic ED group ($n = 12$)	p Value
Post-treatment Intercourse Satisfaction Score	10.3 ± 2.2	7 ± 2.6	8.4 ± 2.3	.009[a]
Post-treatment total testosterone (ng/dl) mean ± *SD*	550 ± 207.2	340.3 ± 107.5	531.1 ± 118.6	.013[a]

Abbreviation: ED, erectile dysfunction.

[a]Kruskal–Wallis test.

LOH as a clinical and biochemical syndrome forming as the result of ageing in males (Nieschlag et al., 2006). In this syndrome, hypogonadism can be related to primary testicle deficiency (low testosterone, high LH) or hypothalamo-pituitary deficiency (low testosterone, low or inconvenient normal LH) (Huhtaniemi, 2014). This hypogonadism presentation, which is normal in puberty and starts in adulthood in males with developed secondary sex characteristics, causes worsened quality of life and deteriorations in different organs and systems (Wang et al., 2009). In males with clinical LOH symptoms and findings, serum total testosterone level should be measured first. The testosterone range at which replacement treatment should be started has not yet been clarified (Huhtaniemi, 2014). The ISA stated that testosterone replacement treatment was not required at values over 346 ng/dl (12 nM) (Wang et al., 2009).

Pre-treatment testosterone value was 280.7 ± 63.9 ng/dl on average in the patients included in our study, and medical treatment was started to increase their testosterone levels.

Testosterone replacement is the gold standard in hypogonadism treatment in male patients without infertility, and testosterone preparations used for this aim can be used in intramuscular, subcutaneous, transdermal (patch and gel), buccal and oral forms (Corona, Rastrelli, Forti, & Maggi, 2011). However, testosterone replacement treatment has side effects, such as erythrocytosis, sleep apnoea, increasing lower urinary system symptoms, increasing prostate cancer formation risks and gynaecomastia. Therefore, patients should be followed up for these side effects. Conditions such as prostate cancer, haematocrit over 54%, untreated obstructive sleep apnoea, uncontrolled congestive heart failure and unstable angina pectoris are contraindicated conditions for testosterone replacement treatment. Its use is also not recommended in patients who have a PSA level over 4 ng/ml, severe lower urinary system symptom complaints (IPSS Score over 19) and haematocrit over 50%. Although the application of exogenous testosterone in hypogonadism is effective in serum testosterone increase and hypogonadism-related symptoms' recovery, it suppresses hypothalamo-pituitary axis through negative feedback and decreases FSH and LH levels, thus lowering endogenous testosterone production and spermatogenesis. Therefore, its use is not suggested in patients with infertility (Mehta, Paduch, & Goldstein, 2013).

Clomiphene citrate is another drug which can be used to increase testosterone levels (Shabsigh et al., 2005; Whitten, Nangia, & Kolettis, 2006). Clomiphene citrate is a selective oestrogen receptor modulator (SERM) that blocks the negative feedback effect of oestradiol on hypothalamus and thus increases the pituitary release of both LH and FSH (Goldstein, Siddhanti, Ciaccia, & Plouffe, 2000). Publications have claimed that it can be used in male hypogonadism treatment (Shabsigh et al., 2005; Whitten et al., 2006). In a study by Taylor and Levine evaluating 104 patients, testosterone replacement and CC were compared in male patients with hypogonadism, and CC demonstrated biochemical and clinical efficiency with less side effects and a lower cost (Taylor & Levine, 2010). In our study, we applied oral CC treatment with a daily dose of 50 mg due to its low side effect profile, lower cost and similar efficiency to intracavernosal alprostadil in our patients with LOH and vascular ED in light of current studies and observed that total testosterone level increased from 280.7 ± 63.9 ng/dl to 502.13 ± 175.5 ng/dl at the end of the 12-week treatment, and this increase was at a statistically significant level. We discovered that PSA levels increased from 1.68 ng/dl to 1.77 ng/dl, but this increase was not clinically significant although it was statistically significant. Monthly treatment cost of clomiphene was approximately $8.

In addition to the recovery in hormonal parameters, a significant clinical recovery was also detected due to the combination treatment in patients through IIEF-15, EHS, SEP 2 and SEP 3 queries. Average monthly cost of the combination treatment was $34.00. Thus, we believe that the combination treatment is both cost-effective and efficient.

Interestingly, we observed that testosterone level and post-treatment Intercourse Satisfaction Scores demonstrated a significant increase in the penile arterial ED subgroup compared to venogenic ED and mixed ED groups in this study. Penile arterial insufficiency is responsible for 55% of EDs, and in patients irresponsive to treatment with PDE5 inhibitors, severe penile arterial flow insufficiency rate was recorded at 90% (Rogers et al., 2010). Our patient group had an arteriogenic deficiency (pure arteriogenic + mixed) component at a rate of 80.6% (25/31). High treatment success may be related to this condition.

Low patient number, the inability to evaluate partner sexual function and a treatment duration limited to 3 months constitute the limitations of this study.

In PVED patients accompanied by LOH, intracavernosal alprostadil and oral CC combination is an efficient, low cost, and safely applicable and tolerable treatment.

5 | CONCLUSION

Hormonal and penile vasculogenic causes are important in patients with ED. Especially in concurrent LOH and PVED patients irresponsive to PDE5 inhibitors treatment, CC and intracavernosal alprostadil combination treatment may provide significant recovery in sexual and hormonal parameters. This combination treatment is an efficient, affordable and tolerable treatment method. It should be considered that treatment results are slightly improved in PVED, especially in cases of dominant arterial deficiency.

CONFLICT OF INTEREST

None of the authors have any potential conflict of interest.

ETHICAL APPROVAL

All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Consent according to the Helsinki Declaration was taken from Necmettin Erbakan University Meram Faculty of Medicine ethics committee before the study (No: 20202494).

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