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Original Research Article

Assessing the use habits and efficacy of intracavernosal alprostadil: is it tolerable and sustainable?

Mehmet G. Sönmez[1]*, Eren Erol[2], Leyla Ö. Sönmez[1], Arif Aydin[1]

[1]Department of Urology, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey
[2]Department of Neurology, Konya State Hospital, Konya, Turkey

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***Correspondence:**
Dr. Mehmet G. Sönmez,
E-mail: drgiraysonmez@gmail.com

ABSTRACT

Background: The aim of this study was to evaluate the efficacy of intracavernosal alprostadil treatment for erectile dysfunction and the evaluation of factors such as ease of drug use, duration of use, and difficulties in habituation.
Methods: The data of 40 patients who were treated for erectile dysfunction, had inadequate response from first-line treatment modalities, received intracavernosal alprostadil in second-line treatment and continued treatment for more than 12 weeks without interruption were analyzed. Sexual function status was evaluated by 15-question international ındex of erectile function (IIEF-15) form and degree of erection (1-10 points). In addition, duration of use, self-administered dose, reasons for difficulty, and reasons for treatment interruption were investigated.
Results: The mean duration of use was 21.38 months. Patients switched to self-administration after an average minimum dose of 2.23 doses. After 12 weeks, 50% of the patients discontinued self-administration, 10% because of difficulty in administration, 55% because of inadequate erection response, 25% because of time, and 10% because of additional health problems. IIEF-15 parameters and the degree of erection were found to improve significantly after administration ($p<0.05$ for all parameters).
Conclusions: Intracavernosal alprostadil provides significant improvement in sexual function, but since it is an invasive application, patients have difficulty in getting used to it, self-administration is started after a minimum of 2 doses, and the reason for discontinuation is mostly due to inadequate erectile response.

Keywords: Alprostadil, Erectile dysfunction, Intracavernosal treatment, Sexual function

INTRODUCTION

Erectile dysfunction (ED) is the persistent inability to achieve or maintain an adequate quality penile erection.[1] ED is a common disorder and is thought to affect more than 150 million people worldwide.[1,2] Cardiovascular diseases, obesity, smoking, hypercholesterolemia and metabolic syndrome, radical pelvic surgeries, diabetes mellitus, central and peripheral nervous system diseases, anatomical or structural disorders play a role in the etiology of ED.[3-5]

Alprostadil (prostaglandin E1 (PGE1)) is a smooth muscle relaxant and vasodilator belonging to the prostanoids group.[6,7] With this function, it is used in the treatment of patients with erectile dysfunction. Alprostadil is an approved second-line treatment for erectile dysfunction after oral phosphodiesterase-5 inhibitors, which are first-line treatment.[8,9] Alprostadil treatment may also provide an exit strategy for patients with erectile dysfunction before invasive treatments such as prosthesis.[10,11]

PGE1 is a safe and effective treatment option for erectile dysfunction, available by intracavernosal, intraurethral, and intravenous injection routes. After intracavernosal injection, side effects such as penile pain, hypertension, dizziness, headache, swelling in the penis, Peyronie's disease, bruising or hematoma at the localized injection

site, balanitis, bleeding at the injection site and priapism can be seen in approximately 1-10%.[12]

The aim of this study was to evaluate the efficacy of intracavernosal alprostadil treatment for erectile dysfunction and the evaluation of factors such as ease of drug use, duration of use, and difficulties in habituation.

METHODS

Consent according to Helsinski's declaration was taken from the local ethics committee before the study (2494). This study was conducted by collecting retrospective data. Patients admitted to the urology outpatient clinic of Necmettin Erbakan University Hospital (Konya, Turkey) between 2019 and 2022 with complaint of erectile dysfunction were evaluated. A careful and detailed history was taken to rule out psychogenic and neurologic factors, genital examination, especially evaluation of secondary sex characteristics, and general neurologic examination were performed.

Sexual function and the degree of erectile dysfunction were assessed using the 15-question ınternational ındex of erectile function (IIEF-15) questionnaire and the degree of erection (1-10 points). In addition, self-administered doses, reasons for difficulties, and reasons for treatment interruption during the period of use were investigated and recorded.

Alprostadil (Jectera®, Vem Pharmaceuticals, Istanbul, Turkey) application was applied by using 0.5 inch, 27 to 30 gauge needle, avoiding visible veins, by injecting in the dorsolateral direction of the proximal third of the penis. All patients were started with a dose of 10 µg. The first injection was administered by healthcare personnel and the patient was trained to administer it at home before sexual intercourse. Patients themselves administered the drug after the initial dose under home conditions. In patients who did not get the desired response from the 10 µg dose, the dose was increased to 20 µg.

First, power analysis (paired samples t-test) was conducted with the acquired definitive measurements to determine the size of the ideal sampling for the study. The effect size in the power analysis conducted according to IIEF-15 subunit scores (erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction scores) definitive measurements were calculated as d=0.80. The sample size was calculated as a minimum of 5 for the study population when the error level was determined to be 5% and the power value 95%. The study was completed with this sampling because 40 patients were reached during the study period.

Forty patients who were being treated for erectile dysfunction, had inadequate response to first-line treatment modalities, received intracavernosal alprostadil as second-line treatment and continued treatment for more than 12 weeks without interruption were included in the study.

Patients who used alprostadil for less than 12 weeks, were under 40 years of age, had a history of psychogenic and neurologic disease, malignancy, or pelvic or penile surgery were excluded.

Statistical analysis

Statistical analysis was performed with statistical package for the social sciences (SPSS), v. 23.0 statistical software (SPSS, Inc.). Quantitative data were presented as mean±standard deviation (SD). The McNemar test and Wilcoxon signed-rank test were used to analyse the relationship between categorical and quantitative variables before and after treatment. Lastly, a p value below 0.05 was considered statistically significant.

RESULTS

The mean duration of alprostadil use was 21.38 months. It was determined that patients switched to self-administration after a mean minimum of 2.23 doses. After 12 weeks, 50% of the patients discontinued self-administration, 10% because of difficulty in administration, 55% because of inadequate erectile response, 25% because of time, and 10% because of additional health problems (Table 1). In 2 patients who developed additional health problems, patients had to discontinue the drug due to the development of new pathologies affecting the cardiovascular system. Penile pain and burning sensation, numbness and ecchymosis symptoms were found in two patients who discontinued the treatment due to difficulty in administration. IIEF-15 parameters and degree of erection were found to improve significantly after administration ($p<0.05$ for all parameters) (Table 2). Syncope, and penile fibrosis were not detected in any of the treated patients during the follow-up period. Only 2 patients developed priapism during the treatment process.

Table 1: General parameters related to intracavernosal alprostadil use habits.

Parameters	Mean±SD (median), n (%)
Age (years)	62.82±5.25 (44-72)
Duration of use (months)	21.38±12
Self-administered dose	2.23±2 (1-15)
Patients who interrupted alprostadil administration	20 (50)
Reasons for interruption of alprostadil administration	
1- Cost	0
2- Difficulty in implementation	2 (10)
3- Inadequate erection response	11 (55)
4- Time	5 (25)
5- Additional health problems	2 (10)

Table 2: Alprostadil-related changes in sexual function parameters.

Parameters	Pre-treatment	Post-treatment	P value
Erectile function score (IIEF-15)	9.27±4.96	15.4±8.4	0.001
Intercourse satisfaction score (IIEF-15)	3.7±2.6	6.65±3.7	<0.001
Orgasmic function score (IIEF-15)	3.65±2.4	5.58 ±3.2	0.006
Sexual desire score (IIEF-15)	5.7±1.9	6.4±1.8	0.03
Overall satisfaction score (IIEF-15)	4.17±1.7	5.36±2.9	0.04
Degree of erection	2.35±1	5.88±2.4	<0.001

DISCUSSION

Alprostadil acts on erection through different physiological mechanisms. After binding to PGE1 receptors, it activates the cyclic adenosine monophosphate pathway, causing erection in smooth muscle. This pathway also leads to the activation of protein kinase A, which stops intracellular potassium and calcium influx, leading to smooth muscle relaxation. Following smooth muscle relaxation, the cavernosal arteries dilate. Alprostadil can also achieve this goal by acting as a norepinephrine antagonist.

PGE1 increases intracellular cAMP after binding to E-prostaglandin receptors via cortex-bound adenylate cyclase activity. Activation of Maxi K channels (neuronal calcium sensors) alters the influx of calcium ions, causing cell polarity and finally inhibiting noradrenaline and angiotensin II secretion.[12-14]

By these mechanisms, intracavernous alprostadil is beneficial because of its vasodilator properties, which act by relaxing the smooth muscle of the corpus cavernosum and thus increasing the diameter of the cavernous arteries leading to erection. The use of alprostadil by the intracavernous route has shown to be equal or superior in stimulation of erection when compared with other drugs used by intracavernosal routes such as papaverine or with combination therapy of papaverine and phentolamine, linsidomine and topical nitroglycerin. Most patients have been shown to tolerate intracavernosal alprostadil well when used in therapeutic dosages.[8,12,15]

In accordance with the literature, in this study, it was shown that self-administration was started after the 2nd application and the drug could be used for almost 2 years despite being an invasive application. This shows that intracavernosal alprostadil is well tolerated.

Despite this, it was found that half of the patients could not continue treatment. Although this rate is not low, 55% of the reasons for discontinuation were inadequate drug effect, which is the most common reason. This reason is not related to the tolerability of the drug but to its efficacy. In 10% of the patients, difficulties in application and in 25% of the patients, difficulties in time management were the reasons for discontinuation. This was thought to be related to the time dependence of the effect of the drug and the fact that it is an invasive application.

Intracavernosal alprostadil may cause side effects including penile pain, burning, penile fibrosis, priapism, bleeding and ecchymosis.[16] Only 2 of the patients (10%) discontinued the treatment due to penile pain, burning and ecchymosis. This shows that the application has a low side effect profile.

In randomized controlled trials comparing intracavernosal alprostadil and placebo, it was found that the dose-dependent erection response rate was 70-87%, erections were observed within 3 to 45 minutes and lasted approximately 20 to 660 minutes.[17,18]

In another study, it was also found that there was a response rate of >70% in penile swelling and hardness measured by RigiScan.[16] Men with neurogenic ED seem to respond better to intracavernosal alprostadil administration than patients with vasculogenic ED.[19] Intracavernosal alprostadil administration was found to be more effective than intraurethral administration.[20] In different studies, it was also found that clomiphene combined with PDE-5 inhibitors improved the treatment response.[21,22] In this study, in accordance with the literature, intracavernosal alprostadil treatment resulted in significant improvement in all IIEF-15 scores and degree of erection.

The limitations of this study are that the data were collected retrospectively, the number of patients was small, and the follow-up period was less than 2 years.

In summary, intracavernosal alprostadil administration is an easily adaptable, sustainable and tolerable treatment regimen with high therapeutic efficacy. We believe that it should be considered as a good option before penile prosthesis in selected patients who have failed PDE-5 inhibitor therapy.

CONCLUSION

Intracavernosal alprostadil significantly improved sexual function. However, since it is an interventional invasive application, it was found that patients had difficulty in getting used to it, self-administration was started after a

minimum of 2 doses, and the reason for discontinuation of the drug was mostly due to inadequate erection response.

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