Evaluation of the efficacy and patient satisfaction of the intracavernosal alprostadil in the treatment of erectile dysfunction following robot-assisted radical prostatectomy

Robot yardımlı transperitoneal radikal prostatektomi sonrası erektil disfonksiyon tedavisinde intrakavernozal alprostatilin etkinliği ve hasta memnuniyetinin değerlendirilmesi

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Özet

Amaç: Robot yardımlı radikal prostatektomi (RARP) sonrası erektil disfonksiyon (ED) önemli bir problem olup, bu çalışmada ED tedavisinde kullanılan intrakavernozal alprostadilin etkinliğini ve hasta memnuniyetini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: RARP sonrası ED tedavisinde intrakavernozal alprostadil kullanan hastalar retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, operasyon öncesi ve sonrası International Index of Erectile Function (IIEF) skorları ve genel memnuniyeti IIEF form 13. ve 14. soruları ile değerlendirilerek kayıt altına alındı. Tedavi sürecinde gelişen komplikasyonlar, kullanım dozları ve bırakma nedenleri incelendi.

Bulgular: Araştırmaya toplam 34 hasta alındı. Hastaların yaş ortalaması 61.73±5.80 yıldı. Hastaların % 52.9'unda (n=18) preoperatif ED tespit edildi. Hastaların preoperatif, postoperatif 1. ay, postoperatif 3 ay tadalafil kullanımı sonrası ve intrakavernozal alprostadil kullanan hastaların İEFF ortalaması sırasıyla 20.64±3.46, 15.08±2.09, 15.32±2.18, 26.67±2.30' du. Hastaların intrakavernozal Alprostadil kullanma sürelerinin ortalaması 8.20±2.48 ay' dı ve % 70.58'inde tam ereksiyon sağladığı görüldü. İntrakavernozal Alprostadil kullanımına bağlı hastaların, %2.9'unda hematom, %8.8'inde ekimoz, %11.8'inde ağrı gelişti. Hastaların takip süresi içerisinde %73.5'inin ilaca devam ettiği tespit edildi. Hastaların alprostadil tedavisi sonrası istatistiksel olarak anlamlı derecede genel memnuniyetlerinin yüksek olduğu görüldü.

Abstract

Objective: Erectile dysfunction (ED) following robot-assisted radical prostatectomy (RARP) is an important problem. The purpose of this study was to evaluate the effectiveness of and patient satisfaction with intracavernosal alprostadil used in the treatment of ED.

Material and Methods: Patients using intracavernosal alprostadil in the treatment of ED following RARP were assessed retrospectively. Patients' demographic characteristics, pre- and postoperative International Index of Erectile Function (IIEF) scores, and general satisfaction evaluated using questions 13 and 14 of the IIEF form were all recorded. Complications developing during treatment, dosages used, and reasons for discontinuation were investigated.

Results: Thirty-four patients with a mean age of 61.73±5.80 years were included in the study. Preoperative ED was determined in 52.9% (n=18) of patients. The mean IEFF of the patients who used preoperative, postoperative 1st month, postoperative 3 months after tadalafil use and intracavernosal alprostadil was 20.64 ± 3.46, 15.08 ± 2.09, 15.32 ± 2.18, 26.67 ± 2.30, respectively. The mean length of use of intracavernosal alprostadil was 8.20±2.48 months, and full erection was achieved in 70.58% of patients. Hematoma associated with intracavernosal alprostadil use developed in 2.9% of patients, ecchymosis in 8.8%, and pain in 8.8%. In addition, 73.5% of patients continued to take their medication during the follow-up process. Patients' general satisfaction following alprostadil therapy was statistically significantly high.

This study was approved by the local ethics committee of University of Health Sciences, Erzurum Regional Education and Research Hospital (Approval number: 2021/03-58). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

Sonuç: RARP sonrası, intrakavernozal alprostatil tedavisi, tam ereksiyon sağlamada sonuçlarının yüksek olması, düşük komplikasyon oranları ve yüksek hasta memnuniyeti ile iyi bir tedavi seçeneğidir.

Anahtar Kelimeler: Alprostadil, erektil disfonksiyon, robot yardımlı radikal prostatektomi.

Conclusion: Intracavernosal alprostadil therapy following RARP represents a good therapeutic option due to its high success in achieving full erection, low complication rates, and high patient satisfaction.

Keywords: Alprostadil, erectile dysfunction, robot-assisted radical prostatectomy.

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve or maintain penile erection necessary for successful sexual intercourse and is a common disease with a prevalence of up to 53% in men over the age of 40 (1, 2). A normal erection depends on complete equilibrium among psychogenic, hormonal, neurological, vascular, and cavernosal factors. Impairment of any one of these factors results in ED (2). Although the etiology of ED is multifactorial, the vascular component predominates. Hypertension, diabetes mellitus, hyperlipidemia, and smoking, causes of the development of arteriosclerosis, are therefore the principal risk factors for ED (3).

The mechanism involved in ED developing following radical prostatectomy or cystoprostatectomy is generally neurological in origin, but may also be vascular in origin in cases of injury to the pudendal artery and its branches (4). Postoperative ED rates are decreasing due to nerve preservation as techniques improve. However, despite all these techniques, postoperative erectile capacity is known to range between 35% and 60%, depending on the patient's clinical and pathological stage, preoperative erectile capacity, or age (4, 5). Restoration of erectile capacity in the postoperative period takes 12-18 months, and various oral or intracavernosal drugs and penile rehabilitation are employed to shorten this period and prevent cavernosal fibrosis (6).

Intracavernosal agents are used as mono- or combination therapy, in the form of prostaglandin E1 (PGE1), papaverine, phentolamine, vasoactive intestinal peptides, and nitric oxide donors. Alprostadil, is a synthetic form of PGE1. PGE1 stimulated adenylate cyclase with 3'5'-cAMP formation, and inhibits the release of noradrenaline in alpha 1-adrenoceptors by means of presynaptic prostaglandin receptors. In addition, it results in impairment of smooth muscle tone by inhibiting angiotensin II secretion, and membrane hyperpolarization as a result of potassium ion channel stimulation. It also exhibits anti-collagen and thus antifibrotic effects by inhibiting transforming growth factor β1 (TGF-β1) (7).

In parallel to the development of alprostadil monotherapy, PGE1/papaverine/phentolamine combinations are also currently employed. Automatic injectors have been developed for ED patients regarded as suitable for injection therapy in order to make the process and simple and painless as possible and easily follow-up, and to permit long-term use. The purpose of this study was to evaluate the effectiveness of and patient satisfaction with intracavernosal alprostadil used in the treatment of ED following robot-assisted transperitoneal radical prostatectomy (RARP).

MATERIAL AND METHODS

This retrospective, single-center study was performed following receipt of ethical committee approval (2021/03-58). Demographic characteristics and pre- and postoperative International Index of Erectile Function (IIEF) scores were evaluated from patients' files. Patients' general satisfaction was recorded by examining IIEF form questions 13 and 14.

ED patients started on 5 mg tadalafil following radical prostatectomy but not responding or responding insufficiently were started on 5 μg intracavernosal alprostadil due to potential complications and in terms of drug adherence. The dosage in patients with unsuccessful or inadequate attempted sexual intercourse was increased by 2.5 μg at one-day intervals until a successful response achieved. Patients started on intracavernosal therapy were given detailed information about prolonged erection and potential complications, and were invited to attend routine controls once month-

ly in the first three months, and every three months thereafter. Patients whose neurovascular bundles were preserved during RARP were included in the study. Alprostadil therapy was initiated when no response or an inadequate response to oral 5 mg tadalafil therapy for at least three months was achieved. Patients included in the study were selected from a group participating in and completing applied training involving hand-eye coordination and self-injection before starting intracavernosal therapy. Patients with no interruptions to the study protocol were included. Patients unable to perform self-injection, with histories of cardiovascular or cerebrovascular disease, receiving anticoagulant therapy, with drug hypersensitivity, or failing to comply with the study protocol were excluded.

Patients' IIEF scores after intracavernosal therapy were investigated. Complications developing, frequencies of medication use, length of medication use, and reasons for discontinuation if applicable were recorded.

Alprostadil Application Protocol

The site of alprostadil application was first sterilized. Next, injection was performed to a vein-free region in the proximal and lateral penis using a ready-to-use automatic injector system (Cavarject®, Pfizer) with a 29 gauge needle containing 10 μg alprostadil. Application commenced with 5 μg, this being increased by 2.5 μg at one-day intervals in cases with unsuccessful or inadequate sexual intercourse, with a maximum weekly dosage of 20 μg. These were applied to the proximal lateral aspect of the penis, a different region being used at each application. Efforts were made to prevent post-injection bleeding by compressing the needle site.

Statistical Analysis

The research data were analyzed on Statistical Package for the Social Sciences (SPSS) v20 for Windows software. Categorical variables were expressed as number and percentage, and numerical variables as mean plus standard deviation. Suitability for analysis of numerical variables was assessed using the Kolmogorov Smirnov test. The Wilcoxon test was employed for the comparison of numerical variables. P values <0.05 were regarded as statistically significant.

RESULTS

Thirty-four patients were included in the study. The patients' mean age was 61.73±5.80 years, and mean body mass index (BMI) was 27.91±4.16 kg/m². Regulated hypertension was present in 20.5% (n=7) of patients, and no additional comorbidity was detected. Preoperative ED was determined in 52.9% (n=18) of patients.

Bilateral neurovascular bundle preservation was applied to 52.9% of patients, right-side preservation to 29.4%, and left-side preservation to 17.6%. Patients' mean preoperative IIEF score was 20.64±3.46, decreasing significantly to 15.08±2.09 at one month postoperatively (p<0.001). The mean IIEF score among patients using tadalafil for three months was 15.32±2.18. A small but statistically significant difference was detected between mean preoperative IIEF values (p<0.001).

The mean length of intracavernosal alprostadil use was 8.20±2.48 months. The mean IIEF value among patients using intracavernosal alprostadil was 26.67±2.30. The mean IIEF score patients using intracavernosal alprostadil differed significantly from mean preoperative scores, postoperative first month scores and postoperative 3 month scores patients using tadalafil (p<0.001) (Table 1). Full erection was achieved in 70.58% of our patients.

Intracavernosal alprostadil use-related hematoma developed in 2.9% of patients, ecchymosis in 8.8%, and pain complications in 11.8%. Sufficient response was achieved with 5 μg intracavernosal alprostadil in 61.8% of patients, with 7.5 μg in 26.5%, and with 10 μg in 11.7% (Table 2).

Analysis showed that 73.5% of patients continued to use medication during follow-up, 11.8% discontinued drug use for economic reasons, 8.8% discontinued drug use since they no longer felt the need for it, and 5.9% discontinued their medication due to the death of their spouses (Table 2).

Patients' mean satisfaction scores were 7.76±1.63 preoperatively, decreasing significantly to 4.11±0.84 at one month postoperatively (p<0.001). The mean satisfaction score among patients using tadalafil for three months was 4.17±0.90, a significant decrease compared to preoperative satisfaction levels (p<0.001). The mean satisfaction score of patients using intracavernosal

alprostadil was 9.05±1.32, a significant increase compared to preoperative values (p<0.001). A significant difference was detected between tadalafil users' postoperative first and third month mean satisfaction scores (p=0.011). Mean satisfaction scores among patients using tadalafil and among those using intracavernosal alprostadil both increased significantly between one and three months postopertively (p<0.001) (Table 1).

Table 1. Patients' demographic characteristics, pre- and postoperative IIEF, and general satisfaction results

	Min-max(median)	Mean±SD
Age	51-73 (62)	61.73±5.80
BMI	21-36 (28)	27.91±4.16
Preoperative IIEF score	15-26 (20.5)	20.64±3.46
Postoperative 1st month IIEF score	12-19 (15)	15.08±2.09
IIEF values in patients using 3-month postoperative tadalafil	12-20 (15)	15.32±2.18
IIEF values in patients using 3-month postoperative alprostadil	23-30 (27)	26.67±2.30
Length of alprostadil use (months)	3-12 (9)	8.20±2.48
Preoperative (general satisfaction)	4-10 (6)	7.76±1.63
Postoperative (general satisfaction)	2-6 (4)	4.11±0.84
Using postoperative 3-month tadalafil (general satisfaction)	2-6 (4)	4.17±0.90
Using postoperative 3-month alprostadil (general satisfaction)	6-10 (10)	9.05±1.32

IIEF=International Index of Erectile Function

Table 2. Intracavernosal dosages of alprostadil and reasons for discontinuation

	n	%
Alprostadil dosage		
5 µg	21	61.8
7.5 µg	9	26.5
10 µg	4	11.7
Alprostadil use status		
Continuing to use	25	73.5
Discontinuing for economic reasons	4	11.8
Discontinuing due to no longer needing the drug	3	8.8
Discontinuing due to loss of spouse	2	5.9

DISCUSSION

Prostate cancer (PCa) is one of the most common cancers among men in developed countries. ED is one of the most important and most difficult to treat complications of radical prostatectomy performed for local PCa (8). Although postoperative ED rates are decreasing with the development of nerve preserving techniques, it is still an important problem. Patients should be evaluated in terms of ED prior to surgery, and their expectations in the postoperative period and their IIEF scores for therapeutic success must be recorded.

ED is known to develop in 35-60% of men undergoing radical prostatectomy (RP) (4, 5). Phosphodiesterase type 5 inhibitors (PDE5I) are most commonly employed in medical treatment, together with vacuum devices, local or intraurethral alprostadil, low-energy extracorporeal shock wave therapy (Li-ESWT), intracavernosal injections, and combination therapies (6). Alprostadil is used in the form of intraurethral gel or intracavernosal injection in erection evaluation following radical prostatectomy. Alprostadil may be employed in patients in whom oral pharmacotherapy is unsuccessful, or who are contraindicated or intolerant, who have spinal cord injuries, or in ED patients after radical prostatectomy (2). Penile rehabilitation is defined as achieving maximal improvement in erectile function by the use of various medications or devices following RP (9). Penile rehabilitation increases cavernosal oxygenation and prevents irreversible changes in endothelial and smooth muscles (10). Montorsi et al. showed that local alprostadil use in the early postoperative period significantly increased penile function (11). A penile rehabilitation program must be initiated as soon as possible after surgery in order to limit fibrotic changes leading to ED.

The most important risk factors for ED are advanced age, cardiovascular disease, and diabetes mellitus (12, 13). Young age and low BMI are protective factors in terms of ED (14). Studies investigating the effect of age on postoperative erectile function have reported improvement in 70% of patients under 60, in 40% of patients aged 60-65, and in 30% of those aged over 65 (15). The mean age of the patients in the present study was 61.73±5.80, regulated hypertension was present in 20.5% (n=7), but no additional comorbidities were detected. Preoperative ED was also detected in 52.9% of patients.

The first-line treatment in ED is lifestyle changes, with PDE5 inhibitors representing second-line treatment. Alprostadil or papaverine are used in case of PDE5 inhibitor contraindication and/or inadequate response (16). Alprostadil is a synthetic PGE1 form providing smooth muscle relaxation, with reported success rates in ED of 70-80% at dosages of 2,5-20 μg, the dosage being adjusted depending on the patient and the underlying pathology. It can be applied once daily, or at most 1-2 times a week (17, 18). It was first used by Montorsi in 1997 (19). In the present study, alprostadil used in the treatment of ED following RARP achieved a full erection rate of 70.58%.

Due to the difficult nature of intracavernosal therapy, and its side-effects and costs, it is known to be discontinued in 30-80% of cases (20). One study reported a drug discontinuation rate of 31% with close follow-up and free-of-charge drug support (21). In the present study, 73.5% of patients continued with their medication, while 11.8% discontinued it for economic reasons, 8.8% because they no longer felt the need for treatment, and 5.9% due to loss of their spouse.

Intracavernosal alprostadil therapy has a number of side-effects. One study reported an incidence of pain in the injection site or during erection of 11%, hematoma or ecchymosis at 1.5%, priapism (defined as a painful erection exceeding 4 h in duration) at 1.5%, and penile plaque at 2% (21). Another study reported penile pain and priapism at a rate of 6.4% (22). Bearelly et al. reported that plaque or scar formation was 10%, pain 2%, ecchymosis <1%, irritability <1%, headache <1% and tissue damage <1% (17). That study also reported 1.44-inch shortening in penile length in 27% of patients and penile curvature in 20%. Hematoma was present in 2.9% of patients in the present study, ecchymosis in 8.8%, and pain in 11.8%, but no other complications were observed.

Studies comparing intracavernosal injection with oral therapy have reported significant improvements in satisfaction and IIEF scores. Mulhall et al. reported a high IIEF score of 66 ± 5, and Bearelly et al. of 60.0 ± 10.95 (17, 23). In addition, Kucuk et al. reported higher IIEF scores with intracavernosal therapies compared to PDE5I inhibitors (24). Alexandre et al. reported 78% patient satisfaction and that 86% of patients would recommend the treatment, while Bearelly et al. reported patient satisfaction of 88% and that 94% of patients would recommend the treatment (17, 25). Our patients' IIEF scores decreased significantly postoperatively compared to the preoperative period. However, these decreasing IIEF scores increased significantly in patients using alprostadil. The improvement in IIEF

scores among patients using postoperative intracavernosal alprostadil was greater than that in patients using postoperative tadalafil. As shown in Table 1, patients' mean general satisfaction increased significantly following intracavernosal alprostadil therapy.

There are a number of limitations to the present study, including the low patient number and its retrospective and single-center design. However, we think that intracavernosal alprostadil therapy does not occupy a sufficient place in urological practice, and that it requires better investigation in terms of effectiveness, outcomes, and patient satisfaction. We believe that further prospective, randomized control studies are needed on this subject, and that our own findings will make a significant contribution to the current literature.

CONCLUSION

Intracavernosal alprostadil therapy used after RARP is a good option providing good results in terms of achieving full erection, low complication rates, and high patient satisfaction. However, areas requiring improvement are the drug's high costs and high discontinuation rates.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by the ethics committee of the University of Health Sciences, Erzurum Regional Education and Research Hospital (Approval number: 2021/03-58) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; HK, MSA, FB, Data acquisition; HK, MSA, Data analysis and interpretation; MSA, FB, BB, Drafting the manuscript; HK, MSA, FB, Critical revision of the manuscript for scientific and factual content; MSA, FB, Statistical analysis; FB, BB, Supervision; MSA.

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