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ORIGINAL RESEARCH ARTICLE

Topical alprostadil (Vitaros©) in the treatment of erectile dysfunction after non-nerve-sparing robot-assisted radical prostatectomy

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ABSTRACT

Objective: The aim of the study is the evaluation of the efficacy and safety of the treatment with topical alprostadil (Vitaros©) in post-robot assisted radical prostatectomy (RARP) rehabilitation therapy of patients with erectile dysfunction (ED).

Methods: Seventy-four patients were enrolled and underwent non-nerve-sparing RARP. Inclusion criteria: age <75, preoperatively International Index of Erectile Function (IIEF-5) >16, erection hardness score (EHS) ≥2, weekly sexual intercourse ≥1, affirmative answers to Sexual Encounter Profile Question (SEP-Q) 2 and SEP-Q3, Charlson Comorbidity Index (CCI) ≤5, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, no moderate/severe cardiovascular disease.

Results: Vitaros was administered ≥2 twice a week. At month 6, the IIEF-5 decreased from 20.5 preoperative to 18.1 post-treatment. EHS score decreased from a mean of 3.3 to a mean of 3.0. The quality of life score decreased from an average of 5.1 to 2.3. Weekly sexual intercourse decreased from an average of 2.1 to 1.7. Six patients dropped out; 89.7% patients showed a positive SEP-Q2 and 77.8% a positive SEP-Q3. All patients responded positively to Global Assessment Questions (GAQ)-1 and 97% to GAQ-2. Of all 68 analyzed patients, 13 (17.6%) switched to intracavernous injection therapy.

Conclusions: In conclusion, Vitaros may become a viable alternative to common injective therapies in well-selected patients after RARP.

Keywords: Alprostadil, Erectile dysfunction, Impotence, Penile rehabilitation, Prostatectomy, Topical therapy

Introduction

Erectile dysfunction (ED) is a major issue after robot-assisted radical prostatectomy (RARP) for the treatment of localized prostate cancer, even with a nerve sparing (NS) approach, affecting 14%-84% of the men after surgery (1, 2). The incidence of prostate cancer has increased steadily in the last decade (3). Despite technical improvement in surgical procedures (i.e., nerve-sparing surgery, laparoscopic and robot-assisted surgery), many patients still suffer an inability to achieve a satisfactory erection after surgery. Potency rates at 24 months after surgery vary from 63% to 82% of the total number of patients treated with NS RARP (1). Non-nerve sparing (NNS) RARP has the worst potency outcomes, resulting in erectile dysfunction in up to 90% of treated patients (2). The etiology of ED after prostate cancer treatment has been found to be multifactorial. There is evidence that neuropraxia, ischemic and hypoxic insults, fibrotic remodeling, and apoptosis contribute to ED (4, 5).

Neuropraxia ensues due to mechanical stretching of cavernous nerves, thermal injury from electrocautery use and inflammation from surgical trauma (6). In fact, the nerve manipulation itself may induce a decrease in the production of nitric oxide (NO) and an increase of profibrotic factors production (7, 8). Arteriogenic ED may be determined by the unilateral or bilateral transecting of the pudendal arteries during surgery, which can be the sole support of the corpora cavernosa. Hence, their preservation favorably increases potency recovery (9). Venogenic ED is a consequence of fibrosis of the smooth cells determined by the lack of oxygenation after the operation that causes a venous leakage during erection (6). Indeed, fibrosis may be a consequence of a delayed potency rehabilitation after surgery or be a direct effect of the nervous damage after RARP.

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The probability of recovering erections that are satisfactory for intercourse after RARP is inversely associated with patient age, and directly with the extent and number of neurovascular bundles preserved (4, 5, 10). The quality of preoperative erections affects the probability of recovery afterwards, but this effect is less well documented (4, 5).

The treatment of ED after RARP has been shown to improve the quality of life (QoL) and overall satisfaction for both patients and their partners (11). Oral phosphodiesterase type 5 inhibitors (PDE5-I) constitute the first line of therapy in patients undergoing NS RARP. When oral therapy fails, there are second-line treatments, which include intracavernous injection (ICI) of prostaglandin E1 (PGE1), vacuum erection devices, prostheses and topical alprostadil cream. Intracavernosal therapy is often successful in PDE5-I refractory ED (12, 13). Nevertheless, intracavernosal therapy is an invasive procedure that is associated with dropout rates as high as 40%-50% due to pain, priapism, penile fibrosis, hematoma, ecchymosis, or fear of the needle (14-16).

In the present observational study, a prospective cohort of men, treated with NNS RARP, underwent a postoperative rehabilitation protocol with topical alprostadil cream (Vitaros©) in order to evaluate the efficacy and safety of the treatment. This study may lead to the use of topical alprostadil cream as a viable alternative to ICI.

Materials and methods

We prospectively collected data of 74 men who underwent RARP and used topical alprostadil for ED after surgery. The study was in line with the Helsinki Declaration and respected the dictates of good clinical practice. An informed written consent was acquired from each patient. Patients who enrolled were exclusively NNS RARP performed by the same operator with an extensive experience in urological robotic surgery. Treatment administration started at month 1 after surgery with a minimum administration of topical alprostadil for at least twice a week, even without a subsequent sexual intercourse. Alprostadil was not provided from our Center, but was autonomously acquired from the patients. Charlson Comorbidity Index (CCI) was evaluated in the preoperative values. Inclusion criteria were age <75 years, absence of preoperative ED that was evaluated through preoperative International Index of Erectile Function (IIEF-5) >16, preoperative erection hardness score (EHS) ≥2, preoperative weekly sexual intercourse ≥1, affirmative answers to Sexual Encounter Profile Question 2 (SEP-Q2) and SEP-Q3. SEP-Q2 was defined as the ability to insert the penis into the partner's vagina. SEP-Q3 was intended as an erection long enough to have a successful intercourse. EHS is well-recognized criteria for evaluation of ICI, with a maximum score of 4 and a minimum of 1 (17). IIEF-5 was administered in the validated Italian version. Other criteria were Eastern Cooperative Oncology Group (ECOG) scale of performance status ≤1, absence of moderate/severe cardiovascular disease according to the American Heart Association classification. Preoperative QoL and metabolic status were also evaluated. QoL was rated using a visual scale from 0 to 6, with a perfect QoL scoring 0, and the worst QoL scoring 6. EHS, IIEF-5, SEP and QoL were re-evaluated at three and six months after the first administration of topical alprostadil. At the end of the study period, the Global Assessment Questions (GAQs) were also evaluated, and each patient answered according to their perception of the treatment. (i) GAQ-1: "Has the treatment you have taken improved your erection?'', was asked to evaluate the capacity of the treatment to provide a better erectile function. (ii) GAQ- 2 ''Has the treatment increased your chances of starting a sexual relationship?'' asked to investigate the chances of having a complete sexual intercourse. Answers to GAQs were just affirmative or negative. The study had no funding from any pharmaceutical industry and all patients voluntarily bought the drug because they were not compliant at first to ICI and wanted to experience a "less invasive therapy''. Descriptive statistic was used to report patients' characteristics before and after the treatment. Pearson's chi-square and paired t-test statistical analyses were used to evaluate the response to the treatment. Statistical significance in this study was set as $p \leq 0.05$. All data were analyzed with SPSS version 20.0 (SPSS Inc, Chicago, IL, USA).

Results

A total of 74 patients were enrolled, as they fulfilled all the inclusion criteria; however, six patients dropped out from the study and were excluded from the statistical analysis. The dropouts comprised: one patient for referred elevated pain after topical alprostadil administration; one patient with a history of urethral stenosis dropped out for fear of stenosis recurrence; another patient dropped out for the lack of partners; and one patient never started the treatment due to sudden cardiovascular problems. Two patients had poor adherence to the study controls and pre- and post-operative treatment data were incomplete, therefore they did not enter in the statistical analysis. A total of 68 patients were analyzed (Tab. I). Mean preoperative age was 66.9 ± 5.9 years, Body mass index (BMI) was slightly over the normal with a median of 25.6 and interquartile range (IQR) 24.2-28.6. Diabetes was present in 2 patients (2.9%), hypertension in 16 (23.5%), hypercholesterolemia with elevated low-density lipoproteins in 8 (11.8%), hypertriglyceridemia in 6 (8.8%), metabolic syndrome in 2 (2.9%). Four patients (5.9%) had a previous cardiac ischemic attack or a cerebrovascular disease, in particular, three had suffered from past heart attack and one from a stroke. Most patients had a low CCI, which was 2 (2.9%) in 2 patients, 1 in 12 patients (17.6%), and 0 in the others. ECOG was 0 in all patients. Preoperative sexual profile and ED was in line with the criteria, with a positive SEP-Q2 in 62 patients (91.2%), positive SEP-Q3 in 57 patients (83.8%) with weekly sexual intercourse frequency of 2.1 ± 0.8 and a mean preoperative IIEF-5 of 20.5 ± 3.3. The mean EHS score preoperatively presented good results with a mean score of 3.3 ± 1.0. The QoL ratings were 5.1 ± 0.5 preoperative, maybe linked to the anxiety of the oncological disease and the fear of the surgery and its consequences. At first evaluation 1 month after surgery, before starting the treatment, all patients had complete ED, with complete absence of erections. The post-treatment assessment at month 3 showed a good recovery of the erectile function with a positive SEP-Q2 in 60 patients (88.2%), and a positive SEP-Q3 for 51 (75%) patients. Mean IIEF-5 score was 17.8 ± 2.9, mean month 3 EHS score: 2.8 ± 0.8, mean QoL value at month 3: 2.5 ± 1.0, showing an improvement with the

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TABLE I - Pre-operative parameters of study group (n = 68)

Pre-operative data	Vitaros (n = 68)	
Age (y), mean SD	66.9	5.9
Body max index (kg/m^2), median IQR	25.6	24.2-28.6
CCI, median min-max	0	0-2
ECOG PS, median min-max	0	0-0
Diabetes, n %	2	2.9%
Hypertension, n %	16	23.5%
Hypercholesterolemia, n %	8	11.8%
High LDL, n %	8	11.8%
Low HDL, n %	6	8.8%
High triglycerides, n %	6	8.8%
Metabolic syndrome, n %	2	2.9%
Cardiovascular disease, n %	4	5.9%

CCI = Charlson Comorbidity Index; ECOG = Eastern Cooperative Oncology Group; HDL = high density lipoprotein; IQR = interquartile range; LDL = low density lipoprotein.

TABLE II - Outcomes evaluated in pre-surgery time and post-surgery period at 3-6 months of Vitaros treatment

Statistical analysis	Vitaros (n = 68)						P value
	Pre-surgery		Month 3		Month 6		
EHS, mean SD	3.3	1.0	2.8	0.8	3.0	0.9	0.03
IIEF-5, mean SD	20.5	3.3	17.8	2.9	18.1	2.7	0.001
QoL, mean SD	5.1	0.47	2.5	0.9	2.3	0.8	0.0001
Weekly sexual intercourse, mean SD	2.1	0.8	1.6	0.7	1.7	0.6	0.005
SEP-Q2, n%	62	91.2%	60	88.2%	61	89.7%	0.661
SEP-Q3, n%	57	83.8%	51	75.0%	53	77.8%	0.323

NOTE = EHS = Erection Hardness Scale. IIEF-5 = International Index of Erectile Function; QoL = quality of life score; SEP Q2 = Sexual Encounter Profile Question 2. Paired t-test was applied for scalar variables between pre-surgery values and at month 6. Chi-square test was applied for categorical variables between pre-surgery values and at month 6.

TABLE III - Vitaros efficacy evaluated with answers to GAQ-1 and GAQ-2 and adverse events after 6 months of treatment using a descriptive statistical analysis

Vitaros efficacy		Vitaros (n = 68)	
Positive GAQ-1, n, %		68	100%
Positive GAQ-2, n %		66	97.0%
Collateral effects	Painful erection n %	2	2.9%

GAQ = global assessment question.

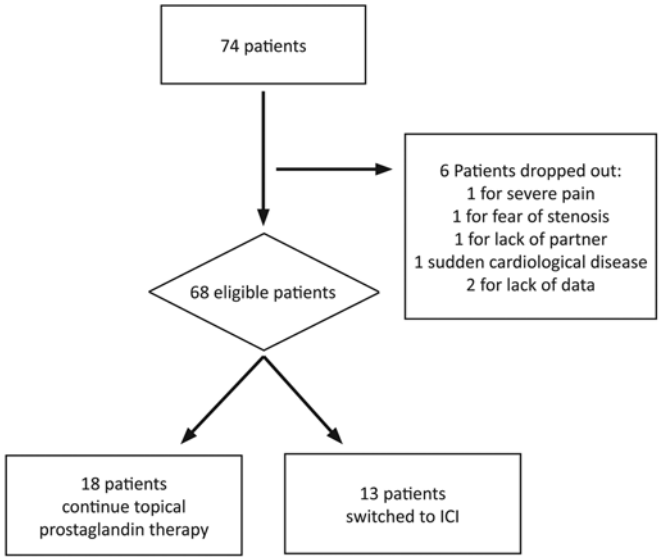

Fig. 1 - Flowchart of study design. ICI = intracavernous injection.

loss of fear of the disease and the progressive recovery of a normal lifestyle, while the weekly sexual intercourse frequency with use of topical alprostadil was 1.6 ± 0.7. At month 6 after therapy, the sexual profile and erectile function showed a further slight improvement as shown in Table II. Collateral effects were low and limited to the first month of therapy, with just 2 patients (2.9%) reporting painful erection, without priapism development as reported in Table III. Statistical analyses were made between the preoperative parameters and the values at month 6. Paired t-test showed a statistically significant reduction in the frequency of weekly intercourse, IIEF-5 and EHS, while QoL showed a statistically significant improvement. Both SEP-Q1 and SEP-Q2 reported no statistically significant difference at Pearson chi-square test evaluation. Of the 74 patients enrolled for the study, 13 (17.6%) eventually switched to ICI, for the preferred more reproducible erections, as they complained of an elevated erection variability with the topical cream, the lower cost of ICI, or for the previously explained reason (Fig. 1). All patients treated gave a positive answer to GAQ-1, while 66 (97%) provided a positive response to GAQ-2 as shown in Table III.

Discussion

ED has been established as a significant contributing factor to sexual discomfort and depression in men years after RARP (18, 19). Even men who are capable of tumescence following RARP lose confidence in their sexual performance ability after frequently failing to achieve and maintain an erection rigid enough for penetration (20).

Several studies have recently elucidated the potential pathophysiology of ED after RARP (7, 8, 21). Wang summarized the mechanism of the way in which chronic impotence reduces blood flow to the corporeal cavernous bodies, which consequently leads to fibrosis and transformation of the trabecular smooth muscle to collagen, which itself leads to the loss of the veno-occlusive mechanism required to maintain

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erections (5). Furthermore, ligation of accessory internal pudendal arteries during prostatectomy decreases arterial inflow, which intensifies hypoxia and ultimately leads to apoptosis of the smooth muscle cells (9).

Of note, men suffering from postoperative ED may also complain of loss of penile length and girth (3). Nowadays, the increased life expectancy of patients undergoing RARP has focused interest in preserving their QoL and avoiding ED. In NNS RARP, this could be achieved only through local therapies or through penile prosthesis.

The rationale for this treatment is the high, virtually immediate effectiveness of the drug in terms of erectile function and especially of hardness, a factor often considered critical to patient satisfaction. Even after NS RARP, neuropraxia involves a period of functional insufficiency of nerve fibers of up to 24 months, thus limiting the effectiveness of the use of PDE-5 inhibitors (22, 23).

The aim of the study is the evaluation of the efficacy and safety of treatment with the use of Vitaros on-demand in post-radical prostatectomy patients.

Alprostadil is a synthetic analog of PGE1. Its mechanism of action involves binding to G proteins coupled to PGE1 receptors on the surface of smooth muscle cells, activating cyclic adenosine monophosphate (cAMP) pathway and thus inducing vascular smooth muscle relaxation and erection. Unlike PDE5 inhibitors, which utilize the NO pathway, alprostadil action, as a direct agonist, means that it can produce erection independently from a stimulus (24).

Novel fatty acid and fatty alcohol esters are employed in alprostadil topical cream. These molecules are chemically and structurally similar to two of the primary skin building blocks: proteins and lipids. These structural similarities temporarily loosen the tight junctions present in skin epithelial cells, allowing for enhanced skin permeation at the site of application, usually the glans penis (24, 25).

Clinical trials have demonstrated that topical alprostadil cream is an effective alternative to the conventional treatment of ED. The first trial was conducted in 1999, where erectile response, skin discomfort, and erythema were measured in 48 men with ED, after the application of topical PGE1 gel in a single-blind, placebo-controlled trial. Utilization of the gel led to an erectile response in 67%-75% patients at varying doses, compared to 17% of controls ($p<0.001$), with no serious adverse events (26).

Our study confirmed that patients with a NNS approach who suffer an almost complete ED after the surgical procedure could benefit from topical therapy. The results demonstrate a statistically significant improvement of erectile function after the treatment, with patients recovering from complete ED. However, the recovery was not complete, with a statistically significant difference between the preoperative values and after 6 months of Vitaros. EHS and the frequency of weekly sexual intercourse suffered a significant reduction. Nevertheless, QoL, which was worse before the treatment probably for psychological reasons, was better after the surgery and the partial recovery of erectile function. However, QoL could also have been affected by incontinence that is bothersome in the first months after RARP, explaining the high variability of the values. In fact, SEP-Q2 and SEP-Q3 were similar to the preoperative values, indicating that Vitaros allowed normal sexual activity. IIEF-5 was still reduced after the therapy, but this is determined by the lack of spontaneous erection and the impossibility to achieve complete sexual intercourse without the treatment. These results are in line with the study of Yiou et al, that demonstrated a partial recovery of erectile function in patients after ICI; however, their study lasted longer, with increasingly better outcomes after a prolonged rehabilitation (27). Literature evidence showed that an early beginning of rehabilitation provided best results with best outcomes when the therapy started one month after surgery, or before month 3. A delayed beginning of ICI was related to a lower recovery rate (28).

In our study, most patients had early rehabilitative therapy that could have affected the outcomes achieved. GAQ-1 and GAQ-2 were almost completely positive, with no patient complaining of an absence of efficacy with the treatment. Patients also had some complications such as previous hypertension, diabetes and cardiovascular diseases that are strictly related to ED, thus increasing the relevance of the obtained outcomes. Complication rate was lower in our data when compared to literature that reported an 11.9% of painful erections compared to our 2.9% (27). Several trials have shown alprostadil cream to be a safe treatment for ED, including the previously described double-blind, placebo-controlled study of 1% alprostadil topical gel, which also examined safety. In fact, in that study, 15 minutes after gel application, significantly greater erythema was reported in the alprostadil group than in the placebo group ($p<0.001$). This was maintained throughout the 90-minute observation period, but reached a peak at 45 minutes after application. Overall, a higher frequency of minimal erythema or a pink uniform discoloration at the application site was observed in the alprostadil versus placebo group (29).

A limitation of the study was the short follow-up and duration of the therapy, because a longer duration of the study may have provided more significant data. It is demonstrated that a prolonged rehabilitation of at least one year provides increasingly better outcomes, even if not comparable to preoperative values (30). In Italy and in our center, post-RARP ED rehabilitation is at no expense to the patients, with drugs provided from the healthcare system. However, Vitaros is not included in the list of drugs provided, so for this reason some patients preferred ICI.

The results of the present study are also affected by several factors that could not be evaluated such as the degree of disease control (because of the possible need for adjuvant treatment), the interest of the patient or his partner in sexual intercourse and urinary incontinence.

It would be interesting to further assess these results with a direct comparison with ICI in a randomized, clinical, controlled trial, in order to evaluate if there is a difference in outcomes, adherence to therapy and collateral effects. Our results are promising, but of course no definitive conclusions can be drawn at this time. Further investigations are mandatory.

Conclusions

Topical alprostadil proved to be an effective treatment for ED following RARP with a NNS approach. At the present time, no definitive conclusions could be drafted over the best

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treatment to propose to patients to treat ED, but Vitaros may be a viable alternative to patients who do not tolerate ICI.

Disclosures

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