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Efficacy and safety of avanafil 200 mg versus sildenafil 100 mg in the treatment of erectile dysfunction after robot-assisted unilateral nerve-sparing prostatectomy: A prospective multicentre study

Pier Andrea Della Camera[1], Riccardo Tellini[1], Gianmartin Cito[1], Giulia Rastrelli[2], Mario Maggi[2], Tommaso Chini[3], Cosimo De Nunzio[4], Vincenzo Maria Altieri[5], Sergio Serni[1], Mauro Gacci[1] and Alessandro Natali[1]

Abstract

Phosphodiesterase type 5 inhibitors represent the standard treatment of erectile dysfunction after nerve-sparing prostatectomy. Avanafil is a second-generation phosphodiesterase type 5 inhibitor with a high selectivity for phosphodiesterase type 5 isoform. To date, there are no studies comparing the outcomes of avanafil versus sildenafil in this scenario. In this study, we evaluated the efficacy and safety of avanafil versus sildenafil as a drug for post-prostatectomy rehabilitation. Overall, 160 patients submitted to robot-assisted nerve-sparing prostatectomy for localized prostate cancer at three hospitals were enrolled for the present study. After 6 months of treatment, patients in the two groups showed no significantly different sexual function scores, except for the Erection Hardness Score and Sexual Encounter Profile-Q2 that were higher in the Sildenafil group. Adverse events in the Avanafil group occurred in four (5%) patients and in 16 (20%) patients in the Sildenafil group. According to our experience, in patients undergoing nerve-sparing prostatectomy, penile rehabilitation with avanafil compared to sildenafil showed a lower ability to produce a valid erection in the initial phase of sexual intercourse, a difference that disappears in the continuation of the same. Avanafil showed a greater tolerance profile with a lower rate of AEs and discontinuation of therapy due to AEs.

Keywords

Erectile dysfunction, prostatectomy, rehabilitation, avanafil, sildenafil, impotence

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Introduction

In the last decade, research efforts have tried to reduce surgical invasiveness and improve functional outcomes including preservation of post-operative sexual power after radical prostatectomy (RP) for prostate cancer (PCa). This is pivotal because PCa is increasingly diagnosed at early age, and the impairment of erectile function could severely interfere with quality of life in younger men.[1] Nerve-sparing (NS) prostatectomy allows the recovery of post-operative erection, although the attainment of satisfactory results is conditioned by many factors such as surgical technique and surgeon experience, pre-existent erectile dysfunction (ED) and medical conditions.[2] For these reasons,

[1]Department of Urology, University of Florence, Careggi University Hospital, Florence, Italy
[2]Sexual Medicine and Andrology Unit, Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Florence, Italy
[3]Department of Urology, University of Siena, Le Scotte Hospital, Siena, Italy
[4]Department of Urology, Sant'Andrea Hospital and Faculty of Health Sciences, Sapienza University of Rome, Rome, Italy
[5]Department of Urology, Humanitas Gavazzeni Hospital, Bergamo, Italy

Corresponding author:
Pier Andrea Della Camera, Department of Urology, University of Florence, Careggi University Hospital, Largo Brambilla 3, Florence 50134, Italy.
Email: pierandreadellacamera@gmail.com

even robot-assisted NS prostatectomy, which is the least invasive surgical technique, is often burdened by the onset or worsening of ED.[3] Historically, the treatment of ED after prostatectomy has been represented by injectable prostaglandins,[4] vacuum devices or penile prosthesis. The advent of phosphodiesterase type 5 inhibitors (PDE5i) (tadalafil, sildenafil, avanafil and vardenafil) has provided an oral treatment alternative for patients with post-prostatectomy ED, although the rehabilitation schedule with PDE5i is still a matter of debate.[5] Sildenafil was the first drug of this category approved for the treatment of ED[6] with proved efficacy in patients with ED after RP.[7] Avanafil is a new PDE5i approved for the treatment of ED by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in April 2012 and in June 2013, respectively, but there is little experience in the literature for its use in the post-prostatectomy ED therapy setting. The drug is available as tablets in three different dosages–50, 100 and 200 mg–and in the context of post-operative rehabilitation, it is usually prescribed with a dosage of 100 or 200 mg. To date, there are no studies that directly compare the outcomes of avanafil versus sildenafil in the challenging scenario of penile rehabilitation (PR) after PCa surgical treatment. In this study, we evaluated the efficacy and safety of avanafil 200 mg versus sildenafil 100 mg as a drug for post-prostatectomy NS rehabilitation.

Patients and methods

After institutional review board approval, patients submitted to robot-assisted unilateral NS prostatectomy for localized PCa at three tertiary referral hospitals from January 2016 to September 2017 were considered eligible for the present study. The choice to perform unilateral NS prostatectomy was done pre-operatively according to the side of positive biopsy cores and/or pre-operative magnetic resonance imaging (MRI); in all cases, an intrafascial dissection with a cautery-free approach aiming to avoid the use of both bipolar and monopolar energy was performed, as previously described.[8] Pre-operative inclusion criteria were the following: age at surgery >18 and <70 years, Charlson Comorbidity Index (CCI) $\leqslant 1$, Eastern Cooperative Oncology Group performance status (ECOG) $\leqslant 1$, 15-question International Index of Erectile Function (IIEF-15) $\geqslant 17$, Erection Hardness Score (EHS) $\geqslant 3$,[9,10] positive response to Sexual Encounter Profile (SEP)-Q2 ('Were you able to insert your penis into your partner's vagina?') and SEP-Q3 ('Did your erection last long enough for you to have successful intercourse?'), Sexual Quality of Life (S-QoL) $\leqslant 3$ (rated using a visual analogue scale from 0 to 6, with a perfect QoL scoring 0 and the worst QoL scoring 6) and reporting at least one sexual intercourse every 2 weeks. To limit the bias associated with the diagnosis of prostate carcinoma, patients were asked to respond with reference to 6 months before surgery or before the start of urological examinations. Pre-operative hypogonadism or neurological disorders represented exclusion criteria as well as the presence of penile anatomical abnormalities. In addition, the use of peri-operative chemotherapy, radiotherapy and/or androgen deprivation therapy represented an exclusion criterion. The presence of absolute contraindications to PDE5i was likewise an exclusion criterion. All patients read and signed an institutional review board–approved informed consent form. All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments, and it respected the dictates of good clinical practice. The study had no funding from any pharmaceutical industry, and patients had the drugs free of charge as they were provided by the Italian healthcare system.

Patients were divided according to treatment into two groups: avanafil 200 mg (A group) and sildenafil 100 mg group (S group). Patients started the rehabilitation therapy on the 10th day after surgery with the removal of the bladder catheter. The two drugs were administered with an on-demand regimen, and each patient was instructed to take the medication at least 30 min before the sexual intercourse attempt. Patients were allowed to consume maximum three tablets per week. During the study period, patients were regularly followed up at a dedicated andrologic outpatient clinic in order to monitor the progress of PR programme and identify any side effects related to the treatment. In case of appearance of adverse events (AEs) and/or in case of ineffective treatment, patients were allowed to abandon the study at any time and start a rehabilitation schedule based on intracavernous injection of alprostadil. EHS, IIEF-15, SEP questionnaire and S-QoL assessment were re-evaluated 6 months after the first administration of PDE5i. At the end of the study period, the Global Assessment Questions (GAQs) were also evaluated: 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 and GAQ-2, 'Has the treatment increased your chances of starting a sexual relationship?' was asked to investigate the chances of having a complete sexual intercourse. Answers to GAQs were dummy variables (yes/no). All patients who took the assigned drug (at least once) were included in the final analyses. Primary endpoint of the study was the comparison between the two groups in terms of positive answers to SEP-Q2, Q3 and GAQs and the EHS and IIEF-15 score after 6 months of post-operative therapy. Secondary endpoints were represented by the differences between the two groups of the S-QoL score and AE rates. Continuous variables were reported as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), as appropriated, while categorical variables were reported as the number and percentage. The Student *t* test or Mann–Whitney

Table 1. Pre-operative features of patients.

Variable	Sildenafil ($n = 80$)	Avanafil ($n = 80$)	p value
Age, median (IQR), years	66 (55–72)	64 (57–71)	0.08
BMI, median (IQR), cm	26 (30–21)	26 (32–21)	0.87
Waist circumference, mean (±SD)	103.2 (±14.3)	98.6 (±13.4)	0.04 **($p<0.05$)**
Hypertension, *n* (%)	32 (40)	24 (30)	0.18
Diabetes, *n* (%)	10 (12.5)	13 (16.25)	0.50
Hypertriglyceridemia, *n* (%)	13 (16.25)	9 (11.25)	0.36
Current smokers, *n* (%)	20 (25)	12 (15)	0.11
CCI score 0, *n* (%)	63 (78.75)	60 (75)	0.45
CCI score 1, *n* (%)	17 (21.25)	20 (25)	0.58
Myocardial infarction	8	10	
Diabetes	8	9	
Chronic pulmonary disease	0	1	
Connective tissue disease	1	0	
ECOG score 0, *n* (%)	96 (95)	96 (95)	1
ECOG score 1, *n* (%)	4 (5)	4 (5)	1
IIEF-15, mean (SD)	22.35 (±2.25)	21.80 (±2.1)	0.513
S-QoL, mean (SD)	1.4 (±1.1)	1.04 (±0.85)	0.642
Weekly sexual intercourses, mean (SD)	1.65 (±0.57)	1.03 (±0.45)	<0.001 **($p<0.001$)**
EHS, mean (SD)	3.6 (±0.62)	3.5 (±0.55)	0.867

IQR: interquartile range; BMI: body mass index; CCI: Charlson Comorbidity Index; ECOG: Eastern Cooperative Oncology Group; IIEF: International Index of Erectile Function; S-QoL: Sexual Quality of Life; EHS: Erection Hardness Score; SD: standard deviation.

test was used to compare continuous variables, while Pearson's chi-square test was used to compare categorical variables. Statistical analysis was performed with MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium).

Results

Overall, 231 patients were submitted to unilateral NS robot-assisted prostatectomy during the study period; 171 patients fulfilled the pre-operative inclusion criteria, and 160 patients were finally enrolled in the study. Both groups included 80 patients. The main clinical and demographic features of patients, as well as pre-operative sexual function questionnaires, are shown in Table 1. The characteristics of patients of both groups were comparable, except for the waist circumference that was slightly higher in the S group (103.2 vs 98.6 cm; $p = 0.04$). Only four (5%) patients per group had the ECOG score equal to 1, being limited in strenuous physical activity. In the pre-operative setting, there were no statistically significant differences regarding IIEF-15 ($p = 0.513$), S-QoL scores ($p = 0.642$) and EHS ($p = 0.867$) between the two groups. Surprisingly, we found a statistically significant difference in the number of pre-operative sexual intercourses among the patients of the two groups, with a higher frequency in the S group (1.65 (±0.57) intercourses/week vs 1.03 (±0.45) intercourses/week; $p < 0.001$). During the study period, 12 (15%) patients in the A group and eight (10%) patients in the S group (with a statistically significant difference between the two groups ($p = 0.034$)) discontinued therapy because they had unsatisfactory erections with oral PDE5i and started PR with intracavernous injections of alprostadil. Table 2 reports results regarding sexual function and QoL at 6-month follow-up. During the treatment period, the frequency of drug intake was comparable between the two groups (two (2–3) tablets per week both in the S and in the A groups). After 6 months from the start of PR, patients in the A group showed an average IIEF-15 score of 18.34, while patients in the S group reached an average score of 18.20, without appreciating statistically significant difference ($p = 0.872$). If we examine the Δ variation of the IIEF-15 score between pre-operative and post-treatment evaluation, the entity of change in the reported scores between the two groups is almost overlapping ($p = 0.451$). When considering S-QoL scoring, the A group and S group showed an average score of 3.05 and 2.48, respectively, with a statistically significant difference between the two groups ($p < 0.05$). At the end of the observation period, EHS was significantly greater in the S group compared to the A group (3.05 vs 2.02; $p < 0.0001$). Although burdened by inhomogeneity of the starting sample (F test for equal variance, $p = 0.002$) due to the presence of greater pre-operative sexual activity in the S group, an increase in the number of sexual intercourses was found in the A group during the study period compared to the pre-operative time (1.03 (±0.37) intercourses/week in the pre-operative period vs 1.25 (±0.41) intercourses/week in the post-operative period) while still remaining a statistically

Table 2. Post-operative sexual function features after 6 months of treatment.

Variable	Sildenafil ($n = 63$)	Avanafil ($n = 68$)	p value
IIEF-15, mean (SD)	18.20 (±2.15)	18.34 (±1.68)	0.872
S-QoL, mean (SD)	2.48 (±0.9)	3.05 (±0.76)	0.05 **($p \leq 0.05$)**
Weekly sexual intercourses, mean (SD)	1.67 (±0.49)	1.25 (±0.41)	0.03 **($p < 0.05$)**
EHS, mean (SD)	3.05 (±0.45)	2.02 (±0.72)	<0.001 **($p < 0.001$)**

IIEF: International Index of Erectile Function; S-QoL: Sexual Quality of Life; EHS: Erection Hardness Score; SD: standard deviation.

significant difference ($p = 0.03$) with respect to the S group (1.67 (±0.49) intercourses/week in the post-operative period). Similarly, the evaluation conducted on the frequency variation of the sexual intercourses per week between the pre-operative and the post-operative period in both groups showed a statistically significant difference in terms of increase of weekly sexual intercourses in favour of the A group ($p = 0.004$). At post-operative sexual function assessment after 6 months of PR, 72 (90%) patients of the S group versus 58 (72.5%) patients of the A group answered positively to the SEP-Q2 test ($p = 0.022$), while, in reference to the SEP-Q3 test, almost the same percentage of patients of both groups, 75% (60 patients) in the S group versus 72.5% (58 patients) in the A group, gave a positive answer ($p = 0.857$). Moreover, 76 (95%) patients of the S group and 68 (85%) patients of the A group answered positively to the GAQ-Q1 test ($p = 0.065$), and 76 (95%) patients of the first group and 70 (87.5%) patients of the latter group answered positively to the GAQ-Q2 test, respectively, ($p = 0.161$). AEs occurred in 16 (20%) patients in the S group and in 4 (5%) patients in the A group. Of those patients, only nine in the first group discontinued drug therapy, while no patients in the A group had to suspend therapy; this for reducing symptoms after repeated administration or for patient sustainability of symptoms (Table 3). The most common side effect in both groups was headache followed by flushing. Myalgia, cyanopsia and dyspepsia occurred only in patients belonging to the S group, as shown in Table 3.

Table 3. Adverse events.

Adverse events			
Sildenafil, *n* (%)	16 (20)	Avanafil, *n* (%)	4 (5)
Type of adverse events	Sildenafil	Avanafil	
Headache, *n* (%)	8 (10)	4 (5)	
Flushing, *n* (%)	6 (7.5)	1 (1.25)	
Myalgia, *n* (%)	1 (1.25)	0 (0)	
Cyanopsia, *n* (%)	1 (1.25)	0 (0)	
Dyspepsia, *n* (%)	3 (3.75)	0 (0)	

Discussion

The success of NS prostatectomy is based on the preservation of sexual activity in the post-operative period. During the operation, neuropraxia is inevitable, despite technically advanced surgical techniques for RP, and the damage of the nerves of the pelvic plexus that surrounds the sides of the organ can lead to ED. Neuropraxia is an event linked to the stretching of the nerves during the isolation of the gland, both to the thermal damage of the electrosurgical unit and to the coagulation of the pudendal plexus branches that supplement the nerve structures. Although discussed in the literature, for the reasons just mentioned, prostatectomy sexual rehabilitation aims at interrupting this cascade of events that can increase or lead to sexual dysfunction. The beneficial effect of PDE5i on restoring the neurovascular injury that occurs during prostatectomy has been widely demonstrated both in vitro [11] and in vivo[12,13] with several PDE5i. Sildenafil was the first drug of this group approved for the use in PR after RP, and several series reporting safety and efficacy have been reported so far.[14] Avanafil, instead, has been introduced in clinical practice in 2012, and numerous series reported its safety and efficacy in general population, but evidence is lacking in the scenario of PR after RP. The only study available so far is that of Mulhall et al.[15] that randomly administered 200- or 100-mg avanafil or placebo to patients submitted to bilateral NS-RP. In this important work, after 12 weeks of treatment, there was a statistically significant difference in terms of the erectile function domain of the International Index of Erectile Function questionnaire (IIEF-EF), SEP-Q2 ('Were you able to insert your penis into your partner's vagina?') and SEP-Q3 ('Did your erection last long enough for you to have successful intercourse?') scores in patients receiving both 200- and 100-mg avanafil compared to placebo. In the same study, the reported rate of AEs was low and no severe AEs were observed. To the best of our knowledge, the present study reports the first head-to-head comparison between avanafil and sildenafil in the clinical context of PR after NS-RP. In our study, after 6 months of treatment, we found superimposable results in terms of the IIEF-15 score between the two groups but significantly greater results for the S group in terms of the EHS score. This finding suggests that sildenafil may be more effective than avanafil in producing a valid erection. This result seems to be strongly related to the differences in terms of the

positive answer rate, greater in the S group, to SEP-Q2 that assesses the ability to start a sexual intercourse. On the contrary, at the end of the observation period, positive answers to SEP-Q3, that evaluates the ability to complete a sexual intercourse, were comparable between the two groups. On the basis of these findings, it could be supposed the existence of an intersubjective variability that influences the response to different PDE5i and consequently the chances of obtaining valid erections. Interestingly, the SEP-Q3 score was similar between the two groups at the end of the observation period, underlining the same efficacy of the two drugs in completing a sexual intercourse, when a valid erection has been reached. The less efficacy in terms of EHS and SEP-Q2 shown by avanafil compared to sildenafil justifies the higher rate observed in the A group in terms of switch from the oral therapy to intracavernous PR with alprostadil. Unexpectedly, the frequency of sexual intercourses in the pre-operative period was significantly higher in the S group than in the A group. After 6 months of PR, the frequency of attempts at sexual intercourses was increased in the A group compared to the same group in the pre-operative period (1.25 vs 1.03 intercourses/week), while in the S group, the frequency of sexual intercourses in the post-operative period was comparable to that in the pre-operative period (1.67 vs 1.65 intercourses/week). At first sight, this finding seems to disagree with the previously reported results in terms of EHS and SEP-Q2 scores, and it can only partly be explained by the high satisfaction rate and compliance to the protocol recently reported by Siena et al.[16] in case of free access to the PR protocol, as in the case of our study cohort. More likely, this finding should be put in relation to the excellent safety and tolerance profile shown by avanafil (only 5% of patients showed AEs with no patients who had to interrupt the treatment due to severe AEs) that mainly depends on its high selectivity for PDE5 subtype.[17] The present study is not devoid of limitations. An important limitation of our work is that there was no assessment of post-operative incontinence which may have an importance in quality of life evaluation. Nevertheless, 6 months after surgery, in our work, most patients in both groups had at least minimal stress incontinence and most carried a pad just for their own safety. No patient reported incontinence, limiting daily activities or requiring intensive pelvic floor rehabilitation or further surgery (data not shown). Indeed, although a robot-assisted approach was used in all cases, no information is available on surgeon's experience that may have affected post-operative outcomes. Finally, our series is composed by patients submitted to unilateral NS prostatectomy that is known to be associated with worst sexual outcomes compared to bilateral NS technique;[18] for this reason, our results may not be generalizable to patients submitted to bilateral NS surgery. However, the present study shows many strengths. It is the first study directly comparing the safety and efficacy of avanafil versus sildenafil in the context of PR after prostatectomy. Larger studies are needed to confirm our results.

Conclusion

According to our experience, in patients undergoing robotic NS prostatectomy, PR with avanafil 200 mg compared to sildenafil 100 mg showed a lower ability to produce a valid erection in the initial phase of sexual intercourse, a difference that, however, disappears in the continuation of the same. Avanafil showed a greater tolerance profile with a lower rate of AEs and a lower rate of discontinuation of therapy due to AEs.

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ORCID iDs

Riccardo Tellini https://orcid.org/0000-0003-2189-5352
Gianmartin Cito https://orcid.org/0000-0001-7526-4025

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