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ORIGINAL ARTICLE

# A comparison of different oral therapies versus no treatment for erectile dysfunction in 196 radical nerve-sparing radical prostatectomy patients

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We retrospectively analyzed the effects on the erectile function (EF) of no treatment (NT), and an oral therapy (OT; on-demand therapy (OD) or a regimented rehabilitation (RR) program with phosphodiesterase type 5 inhibitors (PDE5-Is)), in a cohort of 196 consecutive patients following nerve-sparing radical retropubic prostatectomy (NSRRP). Patients undergoing bilateral NSRRP (BP; $n = 147$) and unilateral NSRRP (UP; $n = 49$), chose between OT (PDE5-Is OD or RR program) and NT. Patients who chose OD therapy received PDE5-Is (100 mg sildenafil, 20 mg tadalafil and vardenafil), whereas patients who chose the RR program received 100 mg sildenafil or 20 mg vardenafil three times a week, or 20 mg tadalafil twice a week at bedtime. The *t*-test for unpaired data and Fisher test were used for univariate analyses, logistic regression multivariate analysis was used to test the accuracy of available variables to predict EF recovery after radical prostatectomy. Potency rates were significantly correlated with the surgical technique and with OT when compared to NT ($P < 0.02$), respectively 68.7% for BP (61% with no therapy and 71% with PDE5-Is) and 44% for UP (29% with no therapy and 51% with PDE5-Is), while no statistically significative differences were found between OD and rehabilitation protocols (72% with rehabilitation and 70% with OD therapy in BP, 52% with rehabilitation and 50% with OD therapy in UP; $P = NS$). Early OT with PDE5-Is (OD or RR program) was superior to NT in recovery of EF in NSRRP. Furthermore, an RR program with PDE5-Is did not appear to be superior to OD therapy.

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## INTRODUCTION

As prostate cancer is being detected at a younger age and earlier stage, an increasing number of relatively young men are facing the prospect of living with erectile dysfunction (ED) following radical retropubic prostatectomy (RRP).[1,2] The incidence of ED after nerve-sparing RRP (NSP) depends on the age of the patient, erectile function prior to surgery, pre-existing medical conditions, the surgical technique and the surgeon's experience.[3–6] However, it appears that a number of pathophysiological mechanisms are also implicated in ED following RRP, and nerve-sparing techniques alone have been shown to be insufficient for preserving erectile function.[7] The concept of penile rehabilitation in addressing ED after RRP was first explored by Montorsi *et al.*,[8] who used intracavernosal injections of the prostaglandin E1, alprostadil, soon after surgery to accelerate the return of spontaneous erections, followed by the use of oral phosphodiesterase type 5 inhibitors (PDE5-Is) by Schwartz *et al.*[9] Since these initial steps, further research has explored the concept of penile rehabilitation, focusing on the use of pharmacotherapy to minimize the damage involving the cavernosal tissue via preservation of adequate oxygenation, and protection of the endothelia and smooth muscle after injury to the cavernous nerves. Studies in animals[10–12] and initial studies in humans[8,13,14] provide support for penile rehabilitation.[4,7,15] Interest has also been growing in the use of regimented rehabilitative programs rather than on-demand therapy.[1] However, the conclusions drawn from some of these studies have been criticized, mechanisms remain unclear, and evidence supporting penile rehabilitation and a rationale for the use of rehabilitation protocols are not available from large, multicentre placebo-controlled trials.[7] These factors make the issue of penile rehabilitation a major controversy in sexual medicine at the current time.[7,15] Despite this ongoing controversy, supportive evidence from animal studies continues to emerge,[16] and there is evidence that penile rehabilitation is widely used in everyday clinical practice.[17] Giuliano *et al.*[18] explored practice patterns of French urologists and found that >88% used some form of early therapy after RRP, such as regular intracavernous injection (ICI) for rehabilitation (39%), ICI on demand for intercourse (30%), PDE5-Is on demand (16%) or regular PDE5-Is for rehabilitation (8%), alternating ICI and PDE5-Is (7%) and vacuum devices (<1%).

Aim of our study was to retrospectively analyze the effects on potency of no treatment, on-demand therapy and the regimented rehabilitation program after NSP in a single referral center.

## MATERIALS AND METHODS

### Patients

For the specific aim of this study we retrospectively reviewed the clinical, pathological and sexual data from 196 consecutive patients who underwent NSP, 147 bilateral (BP) and 49 unilateral (UP), using an antegrade retropubic approach, between February 2004 and January 2006. Table 1 lists the preoperative characteristics for the two groups of patients. The surgical technique used was our previously described modified antegrade retropubic approach,[19] based on the original method described by Campbell.[20] All patients provided written, informed consent. The study was conducted in accordance with the International Conference on

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**Table 1.** Clinical presentation, baseline characteristics, pathological findings, and survival of the 196 patients

| *Variable* | *Bilateral NSRRP Overall* | *Unilateral NSRRP Overall* | P-*value* |
|---|---|---|---|
| Number of patients | 147 | 49 | / |
| Age (years), mean (range) | 62.2 (43–71) | 63.1 (48–75) | NS |
| Preoperative IIEF-5, mean ± s.d. | 22.8 ± 1.4 | 21.6 ± 2.1 | NS |
| *PDE5-Is preoperative use* | *n* (%) | *n* (%) | <0.05 |
| Yes | 37 (25) | 8 (16) | |
| No | 110 (75) | 41 (84) | |
| Partner's mean age (years) | 57.1 | 56.8 | NS |
| *Comorbidity* | *n* (%) | *n* (%) | NS |
| Hypertension | 9 (6) | 5 (10) | |
| Hyperlipidemia | 10 (7) | 4 (8) | |
| Ischemic heart disease | 2 (1) | 1 (2) | |
| Diabetes | 5 (3) | 2 (4) | |
| LOH | 0 | 0 | |
| *Preoperative PSA (ng/ml) mean (range)* | 7.57 (1.4–15.2) | 8.66 (3.07–20.34) | 0.04 |
| *Biopsy Gleason Score* | *n* (%) | *n* (%) | NS |
| 2–6 | 123 (84) | 34 (69) | |
| 7 | 22 (15) | 12 (25) | |
| 8–10 | 2 (1) | 3 (6) | |
| *Specimen Gleason Score* | *n* (%) | *n* (%) | NS |
| 2–6 | 79 (54) | 19 (39) | |
| 7 | 51 (35) | 24 (49) | |
| 8–10 | 17 (11) | 6 (12) | |
| *Pathological stage (TNM 1997)* | *n* (%) | *n* (%) | |
| pT2 | 100 (68) | 22 (45) | 0.04 |
| pT3a | 39 (27) | 21 (43) | |
| pT3b | 5 (3) | 3 (6) | |
| pT4 | 2 (1.5) | 1 (2) | |
| N+ | 1 (0.5) | 2 (4) | |
| PSA relapse | *n* (%) | *n* (%) | NS |
| Free | 133 (90) | 44 (94) | |
| In relapse | 14 (10) | 3 (6) | |

Abbreviations: IIEF-5, International Index of Erectile Function-5; LOH, low on health; ND, not determined; NSRRP, nerve-sparing radical retropubic prostatectomy; PDE5-Is, phosphodiesterase type 5 inhibitors; PSA, prostate-specific antigen; TNM, tumor–node–metastasis.



Harmonisation and Good Clinical Practice (ICH-GCP) guidelines and the principles of the Declaration of Helsinki.

### Preoperative potency

Erectile function was assessed preoperatively and at 24 months after surgery by the five-item version of International Index of Erectile Function-5 (IIEF-5) questionnaire.[21,22] We evaluated potency at 2 years for score ⩾22 at the IIEF-5 questionnaire.[23]

All 196 patients enrolled in both surgical groups (UP and BP) had mild to normal preoperative erectile function, wanted to resume sexual activity after surgery and had been in a stable, heterosexual relationship for the past 6 months. Mean preoperative potency measured by IIEF-5 was 22 among patients who underwent either UP or BP, indicating that the patient populations in the two studies had similar potency prior to surgery ($P$ = NS).

Vascular comorbidity (hypertension, hyperlipidemia, heart disease and diabetes) was assessed. Furthermore, no neurological comorbidity or LOH were reported (Table 1).

### Disease staging

Preoperative staging was conducted according to the 2002 TNM (tumor–node–metastasis) classification and evaluated using prostate-specific antigen (PSA) levels, digital rectal examination and transrectal ultrasonography with a prostate biopsy. Pathological staging was performed according to the 2002 American Joint Committee on Cancer staging system. All results were stratified according to the type of surgery performed. Biochemical relapse was defined as the evidence of PSA > 0.2 ng/ml in two consecutive measurements.

### Rehabilitation protocols

All patients were informed about the potential benefits of using an oral therapy with PDE5-Is to facilitate the recovery of erectile function postoperatively, and provided with information about the option of on-demand versus consecutive regimented oral therapy. The treatment was started 15 days after surgery when the urinary catheter was removed. Patients were given the choice of joining one of the three different treatment groups: no treatment (group A), PDE5-Is on demand (group B) or within a regimented rehabilitative program (group C). Patients were assigned to one of these groups, depending exclusively on their choice. Patients in group B received PDE5-Is at the dose of 100 mg for sildenafil, 20 mg for tadalafil and 20 mg for vardenafil to be taken as required. Patients in group C received 100 mg of sildenafil or 20 mg of vardenafil three times a week, or 20 mg of tadalafil twice a week; patients were instructed to take these medicines at bedtime.

### Statistical analysis

The Chi Square test was used for univariate analyses and logistic regression multivariate analysis was used to test the accuracy of commonly used pre and postoperative available variables (age, PSA, biopsy and pathological Gleason score, clinical and pathological stage and surgical margin) to predict erectile function recovery after radical prostatectomy. All analyses were obtained using the Stat View 5.0.1 (SAS Institute, Cary, NC, USA).

## RESULTS

Between February 2004 and January 2006, 196 patients underwent RRP using our previously described technique.[19] The mean age of the patients was 62.5 years, with a range of 43–75 years (s.d. = 6.11). Mean follow-up was 23 months (range 3–52). Overall, 177 patients (91%) showed no signs of biochemical relapse. Preoperative PSA levels were as follows for the two surgical groups: a mean of 7.57 ng/ml (median 7.05, s.d. 3.17 and range 1.4–15.2) for patients who underwent BP and a mean of 8.66 ng/ml (median

8.00, s.d. 3.91 and range 3.07–20.34) for patients who underwent UP ($P<0.05$). The overall incidence of positive surgical margins was 5.6% (11/196), and more specifically, 6.1% (9/147) for BP and 4% (2/49) for UP ($P=0.289$). Table 1 illustrates preoperative clinical and pathological staging and Gleason score by type of nerve-sparing technique.

### Postoperative potency

At 24 months, potency rates using the IIEF-5 score were significantly correlated with surgical technique; 68.7% for BP (61% with no therapy and 71% with PDE5-Is) and 44% for UP (29% with no therapy and 51% with PDE5-Is; $P<0.02$) as reported in Tables 2 and 3. Potency rates were not significantly influenced by the type of oral treatment (on-demand or regimented rehabilitative program) but we found that oral therapy was significantly correlated with higher recovery of potency rates when compared to no treatment ($P<0.02$; Tables 2 and 3). No statistically significant difference was found when potency was assessed for the oncological outcome (free from progression versus PSA relapse) and for the Gleason score. Although statistically significant, the two-year difference in age observed for the 'younger (61.6 years)' and 'older (63.5 years)' patients are unlikely to be physiologically significant ($P=0.03$). Multivariate analyses showed that age, bilateral or monolateral surgery and stage were significantly associated with recovery of potency after surgery.

At univariate analysis only preoperative PSA, age and pathological stage ($P=0.049$, 0.05 and 0.041, respectively) resulted statistically related to postoperative potency. Subsequent to univariate analysis, we performed the logistic regression multivariate analysis, and PSA ($P=0.047$), age ($P<0.001$) and pathological stage ($P<0.001$) were confirmed as independent predictive factors for postoperative potency (as reported in Table 4).

### Discontinuation of therapy

Overall, 33.56% of patients (49/146) who received PDE5-Is discontinued therapy, and specifically, 29% of patients (32/111) who underwent BP and 49% (17/35) of those who underwent UP. Among the 49 patients who discontinued PDE5-Is, the reasons reported were as follows: 89.8% (44/49) claimed that the effect of therapy was below their expectations, and 8.16% (4/49) of patients or their partner 2.04% (1/49) showed a loss of interest in sex. No patients discontinued PDE5-Is due to side effects.

## DISCUSSION

This is a retrospective analysis of the effects of no treatment and early penile therapy with PDE5-Is (on-demand compared with a regimented rehabilitative program) on potency during the postoperative period following NSP in a cohort of 196 consecutive patients. Comparisons between findings from this study and published data are complicated by a number of issues, including surgical expertise, differences concerning erectile function measurement, the starting time of drug therapy and compliance with oral therapy after surgery, the use of an on-demand or a regimented consecutive PDE5-Is rehabilitative program and lastly, the patients' age. Surgical expertise is one of the most significant factors influencing the occurrence and severity of ED among patients undergoing RRP and the preservation of erectile function following RRP by experienced surgeons at centers of excellence is

**Table 4.** Univariate (Chi square test) and multivariate (logistic regression model) analysis of pre- and postoperative variables and potency recover after prostatectomy

| *Variables* | *Univariate analysis* | *Multivariate analysis* | | |
|---|---|---|---|---|
| | *P-value* | *P-value* | *Risk ratio* | *95% CI* |
| Preoperative PSA | 0.049 | **0.047** | 1.128 | 1.000–1.272 |
| Age | **0.05** | **0.001** | 1.178 | 1.091–1.273 |
| Biopsy GS | NS | | Not included | |
| Clinical stage | NS | | Not included | |
| Pathological stage | **0.041** | **0.001** | 1.178 | 1.091–1.273 |
| Surgical margin | NS | | Not included | |

Abbreviations: CI, confidence interval; GS, Gleason score; PSA, prostate-specific antigen. Bold values are significant values.

**Table 2.** Potency status according to type of therapy among patients who underwent bilateral NSRRP ($n=147$)

| | *Bilateral NSRRP* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Overall* | *NT* | *OT* | *P-value* | *RR* | *OD* | *P-value* |
| Number of patients | 147 | 36 | 111 | / | 88 | 23 | / |
| Potent | 101 (69) | 22 (61) | 79 (71) | <0.02 | 63 (72) | 16 (70) | NS |
| Discontinuation of treatment | 46 (31) | 14 (39) | 32 (29) | / | 25 (28) | 7 (30) | / |

Abbreviations: ND, not determined; NSRRP, nerve-sparing radical retropubic prostatectomy; NT, no treatment; OD, on-demand therapy; OT, oral therapy; RR, regimented rehabilitation program.

**Table 3.** Potency status according to type of therapy among patients who underwent unilateral NSRRP ($n=49$)

| | *Unilateral NSRRP* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Overall* | *NT* | *OT* | *P-value* | *RR* | *OD* | *P-value* |
| Number of patients | 49 | 14 | 35 | / | 27 | 8 | / |
| Potent | 22 (44) | 4 (29) | 18 (51) | <0.02 | 14 (4) | 4 (50) | NS |
| Discontinuation of treatment | 27 (56) | 10 (71) | 17 (49) | / | 13 (49) | 4 (50) | / |

Abbreviations: ND, not determined; NSRRP, nerve-sparing radical retropubic prostatectomy; NT, no treatment; OD, on-demand therapy; OT, oral therapy; RR, regimented rehabilitation program.

40–85%.[24] In this study, 29% of patients (4/14) who underwent UP and chose no therapy and 61% of patients (22/36) who underwent BP and chose no therapy, were potent at 24 months using the IIEF-5 questionnaire. Conversely, 51% of patients (18/35) who underwent UP and chose therapy and 71% of patients (79/111) who underwent BP and chose therapy were potent at 24 months. These findings indicate that PDE5-Is treatment is superior to no therapy in NSP ($P < 0.02$) as reported in Tables 2 and 3. Regarding to the method of measuring potency, some studies report the return of spontaneous normal erections,[9] and some report erections sufficient for sexual intercourse,[24,25] while others report potency measured using validated questionnaires, such as the IIEF.[21] Our study reports potency at 2 years for score $\geqslant 22$ at the IIEF-5 questionnaire.[23]

Wide variations in the timing of the start of rehabilitation therapy after surgery, and the use of combination and/or consecutive therapy further complicate comparisons. In this study, PDE5-Is were started early (2 weeks after surgery), as soon as the catheter was removed. In a study by Nandipati *et al.*,[26] penile rehabilitative therapy started on the day of discharge from hospital (5–6 days after surgery) and consisted of an early combination of sildenafil 50 mg daily plus intracavernosal injections with prostaglandin E1, 2–3 times a week. In a study by Bannowsky *et al.*,[27] the effect of sildenafil as a rehabilitative program was evaluated among 43 patients in whom spontaneous nocturnal erections were preserved after NSP. A total of 23 patients received a rehabilitative program of sildenafil administered at a dose of 25 mg per night, starting on the day after catheter removal, while the remaining 18 patients were followed but did not receive therapy. Mean preoperative potency (measured using the IIEF-5) was 20.8 in the group who received therapy, and 21.2 in the no-therapy group. These preoperative IIEF scores are similar to the mean preoperative IIEF scores recorded in this study, which were 22 among patients who underwent either UP or BP, indicating that patient populations in the two studies presented similar potency prior to surgery ($P =$ NS). At 12 months, the mean IIEF score was 14.1 and the potency rate was 86% in the therapy group compared with a mean IIEF score of 9.3 and a potency rate of 66% in the no-therapy group. In this study, potency was defined as a mean IIEF score $> 19$, which appears to be a much more stringent definition of potency than that used by Bannowsky *et al.*

Using this definition, 52–72% of patients (14/27 UP patients and 63/88 BP patients) who underwent NSP and subsequently received sildenafil in a rehabilitative program were potent compared to 29–61% who received no therapy (4/14 UP patients and 22/36 BP patients).

The only cohort of RRP where patients were counseled to start pharmacological erectile treatment as early as the second month after surgery, gave the best results of potency recovery at 2 years.[28] By contrast, in a study by Katz *et al.*,[29] patients were deliberately asked not to use any erectile rehabilitation after laparoscopic RP, and despite this, there was a high potency preservation rate. In our opinion, as atrophy and fibrosis in the penis occur in the first 3 months after RRP, it is likely that early postoperative intervention is crucial.[2] Moreover, it has been suggested that early postoperative use of ED therapies may play a significant psychological role by addressing the potential disturbance in the sexual relationship that can develop between couples as a result of ED in the period following clinically successful radical prostatectomy.[30] Being able to resume sexual intercourse earlier may be a benefit,[2] and if nothing else, patients may feel that they are doing something to improve their sexual recovery.[7] This means that the need for postoperative therapy should be discussed with the patient prior to surgery, when providing counseling about RRP as one of the treatment options for prostate cancer.[2,30] Appropriate, well-timed education will help patients to make properly informed choices about the treatment of their cancer and any postoperative rehabilitative therapy they may wish to pursue to optimize postoperative erectile function.[30] Compliance with rehabilitative therapy is already emerging as an issue. In a study conducted by Salonia *et al.*,[31] roughly 73% of patients who started on-demand or daily PDE5-Is therapy within 15 days of BP had discontinued therapy at 18 months, for reasons similar to those identified in this study. In a study conducted by Jiann *et al.*,[32] one of the main reasons cited for not using rehabilitative programs was the treatment cost. In the region of Italy where this study was conducted, the cost of therapy is fully reimbursed for patients who undergo RRP for prostate cancer. This means that cost was not an issue for patients considering therapy (on-demand or within a regimented rehabilitation program). In regions and countries where this therapy is not fully reimbursed, cost may be an invalidating issue for patients considering this approach. Regarding to the different potency rate between the use of an on-demand or a regimented consecutive PDE5-Is rehabilitative program, the findings of this study appear to be in line with data published recently by Montorsi.[33] No statistically significant differences in the potency rate were reported in this study between PDE5-Is administered on-demand or within a regimented rehabilitative program. Some studies reported that the recovery of erectile function after NSP is inversely related to age.[24,26] In this study, we confirm that age is significantly inversely related to potency after NSP. The limitations of this study include the fact that it is retrospective, non-randomized, uncontrolled and with a limited number of patients. Data collection continues and it will be possible to analyze greater numbers of patients in the future to confirm or refute the findings reported herein.

## CONCLUSIONS

This retrospective analysis of the effect of early penile therapy (on-demand compared to a regimented rehabilitative program) on potency in the postoperative period after NSP in a cohort of 196 consecutive patients found that oral treatment with PDE5-Is was superior to no therapy in RRP. Furthermore, among patients who underwent oral PDE5-Is treatment, a consecutive regimented program did not appear to be superior to on-demand therapy. Large, randomized, placebo or active control studies are needed to elucidate the optimum postoperative strategy for maximizing potency following NSP.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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