

Sexual Medicine

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Recovery of erectile function after nerve-sparing radical prostatectomy: improvement with nightly low-dose sildenafil

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Accepted for publication 25 October 2007

Study Type – Therapy (case control)
Level of Evidence 3b

OBJECTIVE

To evaluate the effect of low-dose sildenafil for rehabilitating erectile function after nerve-sparing radical prostatectomy (NSRP), as the delay to recovery of erectile function after NSRP remains under debate.

PATIENTS AND METHODS

Forty-three sexually active patients had a NSRP; at 7–14 days after surgery they had a Rigiscan® (Dacomed Corporation, Minneapolis, MN, USA) measurement of nocturnal penile tumescence and rigidity (NPTR). To support the recovery of spontaneous erectile function, 23 patients with preserved nocturnal erections received sildenafil 25 mg/day at night. A control group of 18 patients were then followed but had no phosphodiesterase-5 inhibitors. The International Index of Erectile Function (IIEF)-5 questionnaire was completed 6, 12, 24, 36 and 52 weeks after NSRP.

RESULTS

Of the 43 patients, 41 (95%) had one to five erections during the first night after catheter removal. In the group using daily sildenafil the mean IIEF-5 score decreased from 20.8 before NSRP to 3.6, 3.8, 5.9, 9.6 and 14.1 at 6, 12, 24, 36 and 52 weeks after NSRP, respectively. In the control group the respective scores were 21.2, decreasing to 2.4, 3.8, 5.3, 6.4 and 9.3. There was a significant difference in IIEF-5 score and time to recovery of erectile function between the groups ($P < 0.001$), with potency rates of 86% vs 66%.

CONCLUSION

The measurement of NPTR after NSRP showed erectile function even the 'first' night after catheter removal. In cases of early penile erection, daily low-dose sildenafil leads to a significant improvement in the recovery of erectile function.

KEYWORDS

erectile dysfunction, rehabilitation, nerve-sparing, radical prostatectomy, prostate cancer, nocturnal erection

INTRODUCTION

Loss of sufficient erectile function (EF) is a significant complication of radical prostatectomy (RP), in particular for patients who were sexually active before RP. This applies especially to men aged 55–65 years, who are commonly labelled 'ageing men' but who do not want to lose their EF. The cause of erectile dysfunction (ED) after surgery for prostate carcinoma is usually neurogenic, due to intraoperative injury to the neurovascular bundle, while ED after radiotherapy is mainly of vascular origin, with erectile tissue damage.

If both neurovascular bundles are resected during RP, ED ensues in 90–100% of patients. In a population-based investigation after RP (retropubic/perineal, with/without nerve-sparing, NSRP) only 6.7% of the patients did not complain about ED within the first 2 years (Prostate Cancer Outcome Study) [1]. Walsh *et al.* [2] reported spontaneous erections in 38% of patients 3 months after bilateral NSRP, with a further improvement to 84% after 18 months. Other groups, e.g. Noldus *et al.* [3], reported preserved EF in 90% of men after bilateral and 76% after unilateral nerve preservation at 1 year after RP. In that series of patients treated with bilateral NSRP, 56% (unilateral nerve-sparing 30%) were capable of sexual intercourse with no sexual aids. On taking 50–100 mg sildenafil 'on demand', 75% of patients reported an erection sufficient for sexual intercourse [4]. Sildenafil improves EF, if the nerve supply of the penis remains at least partly intact.

The time required to regain EF after NSRP is unclear, as is its susceptibility to medication and the quality of the erection. Different pathophysiological theories of ED after RP have been discussed. The recovery of EF can take up to 24 months after surgery [5]. However, it is important not to wait inactively until EF is regained, as the lack of oxygenation of the corpora cavernosa can lead to involutional atrophy, due to increasing fibrosis of the smooth muscle [6]. Therefore, the focus of therapy for ED after RP is protection, i.e. preserving and rehabilitating EF using phosphodiesterase-5 (PDE5) inhibitors or intracavernosal injection (ICI) therapy with vasoactive agents, in particular after NSRP.

To devising an optimum treatment for recovery of EF after NSRP, we measured nocturnal penile tumescence and rigidity

(NPTR) in the acute phase, i.e. during the first night after removing the urethral catheter, to assess the organic erectile integrity. In a previous prospective study [7] we reported NPTR in 93% of patients after NSRP. With these results in mind, determined whether rehabilitation of EF could be improved by increasing intracavernosal oxygenation using sildenafil, compared with no treatment.

PATIENTS AND METHODS

In all, 43 patients (mean age 63.6 years, range 54–75) who had been sexually active before NSRP had unilateral (11) or bilateral (32) retropubic NSRP. All procedures were carried out by one surgeon. Preoperative staging showed a locally confined prostate cancer in all patients. The distribution of the final tumour stage after complete histopathological processing was six with stage pT2a, nine pT2b, 18 pT2c, eight pT3a and two pT3b. The EF before NSRP of all patients was evaluated using the International Index of Erectile Function (IIEF)-5 questionnaire. At 7–14 days after NSRP the indwelling catheter was removed and a NPTR measurement made during the following night, using the RigiScan® device (Dacomed Corporation, Minneapolis, MN, USA). None of the patients received any medication influencing EF during this period.

Patients were then randomized into two different follow-up groups matched by preoperative IIEF score, age, numbers of nocturnal erections and status of NSRP. To maintain and support the recovery of spontaneous EF, 23 patients with preserved nocturnal erections detected during NPTR recordings received sildenafil 25 mg/day at night, starting on the day after catheter removal. A control group of 18 patients with similar numbers of nocturnal erections had no PDE-5 inhibitors. The IIEF-5 questionnaire was then completed at 6, 12, 24, 36 and 52 weeks after NSRP to evaluate the recovery of EF in both groups. None of the 43 patients received hormonal therapy or radiotherapy before or after RP.

The results were evaluated using the Kruskal-Wallis test, Mann-Whitney *U*-test, Student's *t*-test, Fisher's exact test and Pearson correlation.

RESULTS

All patients had an IIEF-5 score of >16 (range 16–25) before NSRP (Table 1). The night

TABLE 1 The distribution of patients according to the IIEF-5 score, and nocturnal erections after uni-/bilateral NSRP (penile rigidity increase >70% over >10 min)

Variable	No. of patients
IIEF score	
<16	0
16–19	6
20–21	13
22–23	18
24–25	6
No. of erections per night, all/unilateral/bilateral NS	
0	2/1/1*
1	7/2/5
2	14/3/11
3	9/2/7
4	5/2/3
5	6/1/5

*Excluded from the further study, treated by ICI therapy.

after removing the catheter, 41 of 43 patients (95%) had at least one nocturnal erection that lasted for >10 min and >70% nocturnal penile radial rigidity at the tip and base, with a mean (SD, range) of 2.7 (1.32, 1–5) erections/night (Table 1).

In two patients (one after uni- and one after bilateral NSRP) the rigidity increase was <70% and <10 min duration, which was deemed insufficient for intercourse. In a control group of patients with no NSRP no nocturnal erections were recorded, as described previously [7].

There was no correlation between the IIEF score before and EF after NSRP ($r = 0.063$, Pearson correlation, $P = 0.804$).

In the 32 patients who had bilateral NSRP, the NPTR measurement showed 31 having a mean (SD, range) of 2.74 (1.32, 1–5) nocturnal erections/night. In the 11 men treated with unilateral NSRP, 10 had intact EF, with 2.70 (1.34, 1–5) erections/night. The difference in nocturnal erections between uni- and bilateral NSRP was not statistically significant ($P = 0.931$).

There was also no significant correlation between the final tumour stage and number of nocturnal erections or rigidity ($P = 0.441$).

FIG. 1. The recovery of EF after NSRP (41 men).

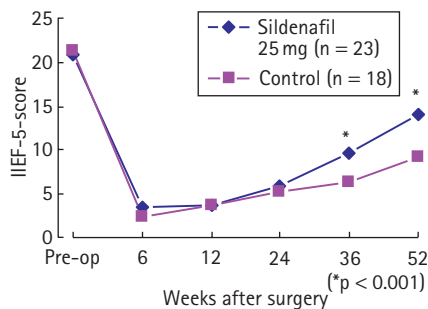
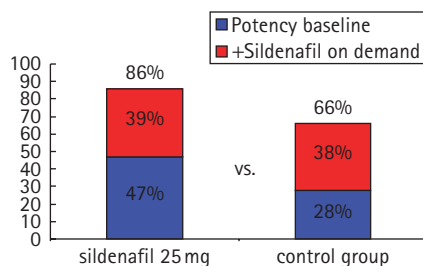


FIG. 2. Potency rate with and without low-dose sildenafil (25 mg) after NSRP.



A valid comparison of the data with the status of nocturnal erections before NSRP was not possible within the study, as sedative medication was administered the night before surgery. During NPTR measurements on the night before NSRP, few to no erections were recorded.

In the men using sildenafil the mean (SD) IIEF-5 score decreased from 20.8 (2.80) before to 3.6 (2.06), 3.8 (1.38), 5.9 (1.84), 9.6 (2.37) and 14.1 (3.03) at 6, 12, 24, 36 and 52 weeks after NSRP, respectively, with no additional sildenafil 'on demand' (Fig. 1). In the control group the respective mean (SD) IIEF-5 scores were 21.2 (2.20), 2.4 (1.89), 3.8 (1.63), 5.3 (2.17), 6.4 (2.08) and 9.3 (2.14), respectively (Fig. 1). There was a significant difference in IIEF-5 score and time to recovery of EF between the groups at 36 and 52 weeks (both $P < 0.001$; Fig. 1). In the group taking sildenafil, 47% achieved and maintained a penile erection sufficient for vaginal intercourse at 1 year after NSRP, with no 'on-demand' sildenafil, compared with 28% in the control group with no low-dose sildenafil. This baseline potency was increased by additional sildenafil (50–100 mg) on-demand, to 86% overall potency in the men taking 25 mg sildenafil vs 66% in the group with no treatment (Fig. 2).

DISCUSSION

Prostate cancer is the most frequent malignant tumour in men. ED and urinary incontinence are the two most severe adverse influences on the quality of life of these patients after surgery. Although the exact process of rehabilitation of EF after RP is not fully understood, the absence of erections soon after RP is associated with unsatisfactory cavernosal oxygenation, which can cause fibrosis of the corpora cavernosa and finally lead to veno-occlusive dysfunction [8]. Experimental animal studies showed the importance of smooth muscle apoptosis in the corpus cavernosum in the context of investigating the pathophysiology of postoperative ED [9].

Erectile rehabilitation takes up to 2 years after surgery, according to published reports [5]. Some authors think that if spontaneous erections do not occur by the 1 year after bilateral NSRP, a technical or surgical-related problem must be the underlying cause [10]. However, that it can take a long time until the first spontaneous erections occur should not lead the treating urologist to wait patiently and inactively. On the contrary, supportive medication should be started to rehabilitate EF as early as possible.

According to previous reports, early therapy, i.e. within the first month or even starting from the day of catheter removal, is recommended either with intracavernosal prostaglandin-1 or oral substitution therapy with sildenafil (or vardenafil or tadalafil) or a combination of both, to support cavernosal oxygenation and to prevent otherwise impeding fibrosis [6,11]. The recovery of EF by using PDE-5 inhibitors might be enhanced by the additional endothelial protection [12]. Schwartz *et al.* [13] reported the preservation of intracorporeal smooth muscle content by the early use of sildenafil after RP. The early introduction of ED therapy also helps to counteract any possible avoidance of sexual activity by the patient, which might develop due to frustrating attempts at sexual intercourse, and that would have an additional counteractive effect.

The question of which of these therapeutic strategies is the most effective for each patient cannot be answered satisfactorily, as the process of rehabilitation of ED is not yet clear. The response rate achieved with

sildenafil, for example, depends very much on the type of surgical technique; the highest response rate was in young men after bilateral NSRP (80%), followed by those with unilateral NSRP (50%), while only 15% responded in patients having no nerve protection [14]. The response rate increases when the period of ED therapy is extended; in the first 6 months after RP only 26% benefit from therapy with PDE-5 inhibitors [4,15], but up to 60% improve and become normal within the first 18 months [15]. Long-term treatment (3 years after RP) produced an overall response rate of up to 71% spontaneous erections with on pharmacological support [16]. The success rate achieved using ICI therapy with vasoactive agents (prostaglandin-1) reached 90% in the first 6 months after RP (provided EF was fully intact before RP) [17].

A better understanding of the pathophysiology of ED after RP, including tissue damage induced by poor corporeal oxygenation, paved the way for the prophylactic use of pharmacological regimens to improve early corporeal blood filling. Montorsi *et al.* [6] showed that with intracorporeal injections of alprostadil two or three times per week early after bilateral NSRP, the rate of recovery of spontaneous erections was significantly higher than with observation alone. Mulhall *et al.* [18] confirmed these data and suggested that the prophylactic use of intracorporeal injections of alprostadil in patients not responding to oral sildenafil resulted in higher rates of spontaneous functional erections and erectogenic drug response 18 month after NSRP. The prophylactic use of a vacuum-constriction device was recently proposed as an early penile rehabilitation programme for promoting adequate cavernosal oxygenation, and thus preventing penile fibrosis [19]. In a prospective randomized trial involving 109 men with ED after RP, 36% who had had NSRP and used a vacuum-constriction device daily (beginning a mean of 4 weeks after RP) reported a return of natural erections at the 9-month follow-up, and 55% of these patients had erections sufficient for successful vaginal intercourse. The rate of treatment discontinuation due to lack of compliance was 18%, after a mean of 3 months of use.

The advent of the use of PDE-5 inhibitors for treating ED has clearly revolutionized the management of this condition. However, the

rationale for using these drugs as prophylaxis is still not well understood. The basic concept is to administer a PDE-5 inhibitor at bedtime to facilitate nocturnal erections, which are thought to have a natural protective effect on the baseline function of the corpora cavernosa. Montorsi *et al.* [4] showed that when sildenafil 100 mg is administered at bedtime to patients with ED of various causes, the overall quality of nocturnal erections, as recorded by NPTR measurement, is significantly better than the overall quality of those achieved after administration of placebo. Padma-Nathan *et al.* [20] reported on the prospective administration of 50 and 100 mg sildenafil vs placebo, daily and at bedtime, in patients having bilateral NSRP. The EF after 36 weeks was significantly better in the sildenafil group, with 27% responders, than the 4% in the placebo group.

Our previous study [7] impressively confirmed preserved EF as early as the first night after catheter removal following NSRP, both after uni- and bilateral NS techniques. It therefore presents an important criterion for assessing the quality of the NS procedure in RP, which has become established as a standard technique in our clinic. Nocturnal erections seem to be crucial role for the recovery of normal EF through regular tissue oxygenation of the corpora cavernosa. It was shown that penile oxygenation is extremely low in the flaccid penis (pO_2 25–40 mmHg), while rising to normal tissue levels during erection (pO_2 90–100 mmHg) [21].

These results formed the basis for a new therapeutic concept ('Kiel concept') developed for optimum re-establishment of EF and satisfying sexual function after NSRP [7]. Patients with preserved nocturnal erections detected during NPTR recordings soon after NSRP took sildenafil 25 mg/day at night. There was a significant difference in IIEF-5 score and time to recovery of EF between the group on daily 25 mg sildenafil and the control ($P < 0.001$), with overall potency rates of 86% and 66% at 1-year after NSRP. Patients with no confirmed erections should begin with ICI therapy to optimize EF. If there are still no spontaneous erections at 2 years, more invasive therapy regimens (e.g. penile prosthesis implantation) must be considered. The 2-year results are obviously of interest, because the present interim analysis reflects only the first year after NSRP.

Our findings are important for an appropriate choice of pharmacotherapy to ensure optimal recovery and 'training routine' for EF. Early penile erections indicate that the cavernous nerve has been well preserved during surgery, thus providing good neuronal integrity; in these cases a PDE-5 inhibitor, e.g. sildenafil, can play a supportive role for organic rehabilitation of the corpus cavernosum.

CONFLICT OF INTEREST

None declared.

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Abbreviations: EF, erectile function; (NS)RP, (nerve-sparing) radical prostatectomy; ED, erectile dysfunction; PDE5, phosphodiesterase-5; ICI, intracavernosal injection; NPTR, nocturnal penile tumescence and rigidity; IIEF, International Index of Erectile Function.