Optimization of sexual function outcome after radical prostatectomy using phosphodiesterase type 5 inhibitors

Yasuhiro Kaiho, Shinichi Yamashita and Yoichi Arai

Department of Urology, Tohoku University Graduate School of Medicine, Sendai, Japan

Abstract: Erectile dysfunction after radical prostatectomy is a major complication affecting postoperative quality of life. For early recovery from postoperative erectile dysfunction, attention has focused on penile rehabilitation using vacuum devices, prostaglandin E1 injection into the corpus cavernosum of the penis or transurethral administration, and oral drugs such as phosphodiesterase type 5 inhibitors. Phosphodiesterase type 5 inhibitors have been used clinically based on the results of animal experiments that showed a preventive effect on fibrosis and loss of intracorporeal smooth muscle. Small randomized studies had reported a benefit from penile rehabilitation using phosphodiesterase type 5 inhibitors after radical prostatectomy. However, the largest trial to date, carried out in 2008, failed to show that daily phosphodiesterase type 5 inhibitor treatment was superior to on-demand phosphodiesterase type 5 inhibitor treatment for erectile function recovery after radical prostatectomy. Thus, debate continues as to its efficacy in humans. Reports on penile rehabilitation using phosphodiesterase type 5 inhibitors have appeared after these negative results, and phosphodiesterase type 5 inhibitors are still widely used as first-line treatment in penile rehabilitation.

Key words: erectile dysfunction, impotence, phosphodiesterase inhibitor, prostatectomy, recovery of function.

Introduction

RP is a widely used operative procedure for patients with prostate cancer, but ED is a major complication that greatly affects patients’ postoperative quality of life. Early diagnosis of prostate cancer has become possible with the increased use of prostate-specific antigen tests, and the number of younger patients with prostate cancer is increasing. Early recovery of postoperative ED is therefore an increasingly important issue. Many reports have confirmed that nerve preservation is effective in early recovery from ED. Walsh and Donker proposed a nerve-sparing procedure during RP, after which many operative techniques have been devised to leave erectile nerve fibers intact. Traditional concepts that nerve fibers responsible for erection run exclusively in the neurovascular bundle on the rectolateral aspect of the prostate have been replaced by the recent concept of the periprostatic nerve network. However, even if nerve preservation is completely successful, nerve fibers sustain some level of damage from traction, dissection, or other manipulations during surgery, and the occurrence of ED for a certain period postoperatively is unavoidable. The postoperative hypoxic environment during that time induces fibrosis of the corpus cavernosum of the penis and irreversible degeneration progresses. Early medical intervention is thought to be necessary to recover postoperative EF. The present review will summarize published studies for optimization of EF recovery after RP, focusing mainly on the role of PDE5i.

Causes of ED after RP

Postoperative ED after RP is caused by nerve and vessel damage during surgery. In animal experiments, damage to the cavernous nerves of the penis is known to decrease nitric oxide production, while also inducing apoptosis of corpus cavernosum smooth muscle, and
producing atrophy and fibrosis of the corpus cavernosum. If the corpus cavernosum smooth muscle becomes fibrotic and its volume decreases, the blockage of blood flow in the cavernous veins of the penis necessary to maintain an erection no longer functions, and blood leaks from the corpus cavernosum, producing what is called a veno-occlusive ED state. In contrast, surgical damage to arter-cordus cavernosum, producing what is called a veno-erection no longer functions, and blood leaks from the in the cavernous veins of the penis necessary to maintain an fibrotic and its volume decreases, the blockage of blood flow 

Inflammatory reactions secondary to surgical trauma, such as thermal energy and mechanical forces, are reported to be a contributing factor to the delay in recovery of EF after RP. Yamashita et al. reported that cavernous nerve dissection enhanced the expression of interleukin-6, which is one of inflammatory cytokines, in the major pelvic ganglion in rat. They also showed that inhibition of interleukin-6 bioactivity attenuated nerve injury-related ED after cavernous nerve dissection, concluding suppression of excess inflammatory responses might be important to improve EF after nerve-sparing RP. To reduce inflammatory injury, Finley et al. achieved clinically regional pelvic cooling (<30°C) with a prototype endorectal cooling balloon during the course of robot-assisted RP, and reported that the locoregional hypothermia improved EF at 15 months after surgery. 

Penile rehabilitation

Penile rehabilitation is defined as “the use of any drug or device at or after radical prostatectomy to maximize EF recovery”. Attempts are made to prevent the degeneration and fibrosis of the corpus cavernosum caused by the inva-sion of the surgery itself or the postoperative hypoxic state by oxygenating the penis from an early stage. The effective-ness of penile rehabilitation using therapy with injection of PGE1 into the corpus cavernosum was reported in a rand-onized study by Montorsi et al. in 1997, and recovery of postoperative EF with regular oxygenation of the corpus cavernosum was show clinically for the first time. The major methods of penile rehabilitation have been the use of vacuum devices, PGE1 injection into the corpus cavernosum, or transurethral administration, and oral administration of PDE5i. Of these methods, oral administration of PDE5i has become the first-line treatment in penile rehabilitation because of its convenient oral administration.

Penile rehabilitation using PDE5i

It is known from past animal experiments that PDE5i act to protect corpus cavernosum tissue, and inhibit apoptosis of smooth muscle cells. In humans, it has been reported that 100 mg of sildenafil every other night after RP pre-served intracorporeal smooth muscle on cavernous biopsy and prevented fibrosis of the corpus cavernosum. In clini-cal trials following these basic studies, small-scale rand-onized studies were carried out and reported the efficacy of daily PDE5i for postoperative EF recovery. Banowsky et al. randomized 43 patients after nerve-sparing RP to either daily sildenafil treatment or no treatment and evalu-ated their recovery of EF using the IIEF-5 scores; they concluded that sildenafil led to a significant improvement in the recovery of EF. Padma-Nathan et al. randomized 76 patients after nerve-sparing RP to double-blind sildenafil (50 or 100 mg) or placebo nightly for 9 months and reported that nightly sildenafil markedly increased the return of normal spontaneous erections.

However, despite the aforementioned basic and clinical studies, a multicenter, randomized, double-blind, controlled comparative trial with 628 participants carried out by Montorsi et al. in 2008, the largest trial to date, failed to show the effectiveness of daily administration of vardenafil from an early postoperative stage. In fact, on-demand PDE5i treatment was found to be more effective in improving EF than daily PDE5i treatment. Thus, consider-ing the trial of Montorsi et al., penile rehabilitation is currently seen as having “unknown effectiveness in humans”. Various problems and weaknesses with the methods and participants in that trial have been pointed out, and re-evaluation in a more rigorous clinical trial is anticipated.

Although opinions skeptical of the effect of PDE5i in penile rehabilitation have remained, PDE5i are still used after RP as the first-line of therapy for EF recovery because of patients’ strong desire to recover from postoperative EF, because of past clinical experiences, and because of the convenience of oral administration. In 2010, PDE5is were used as a penile rehabilitation tool in two small-scale rand-onized studies; a prospective, randomized, trial compared with transurethral administration of PGE1; and a prospective, randomized, controlled, comparative trial with 40 patients, and their effectiveness was reported (Table 1). Recently, a report has appeared that determines the type of patient for whom penile rehabilitation will be effective, and that discusses possible reasons for the lack of a significant difference in the trial by Montorsi et al.

As one possible reason to explain why daily PDE5i treatment was not superior to on-demand PDE5i treatment in the prospective, randomized trial by Montorsi et al., Briganti et al. pointed out that differences in preoperative parameters, such as preoperative age, EF and comorbidity profile, which had been reported as well-known predictors of EF after surgery, might alter the effect of penile rehabilitation on EF recovery. The authors stratified 495 patients with localized prostate cancer treated with retro-
pubic bilateral nerve-sparing RP into three groups according to their risk of postoperative ED: low (age ≤65 years, IIEF score ≥26, CCI ≤1), intermediate (age 66–69 years or IIEF-EF score 11–25, CCI ≤1) and high (age ≥70 years or IIEF-EF score ≤10 or CCI ≥2). In each risk group, the differences in the EF recovery rate among patients left untreated after surgery, those receiving on-demand PDE5i and those treated with daily PDE5i were estimated. The results showed that daily PDE5i use had a significantly higher EF recovery than on-demand PDE5i only in patients in the intermediate risk group, whereas no difference in efficacy was seen between daily PDE5i and on-demand PDE5i in patients with a low risk and a high risk of ED. They concluded that the ideal candidates for penile rehabilitation after surgery are patients at intermediate risk of ED. They speculated that corpus cavernosal function is already undermined before surgery in patients at high risk of ED and could not respond to either on-demand or daily PDE5i treatment, and that the corpus cavernosal function in patients at low risk is sufficient to recover EF with on-demand PDE5i, so that daily PDE5i might not be required.51 The patients in the prospective, randomized trial by Montorsi et al. were young and with full preoperative potency, and they were considered to have a low risk of ED; this is one possible reason why the trial failed to show superior efficacy for daily PDE5i treatment compared with on-demand PDE5i treatment for EF recovery after RP.42 Thus, daily PDE5i treatment might be proven to be effective for early recovery of EF after RP in a large-scale, randomized study that takes into consideration the preoperative parameters that affect postoperative recovery from ED.

Urologists always have to consider a more effective way to optimize sexual function after RP, because sexual function is viewed as important among patients with prostate cancer, and many patients hope for an early recovery of EF after surgery. Although the past large, randomized trial failed to show efficacy, PDE5i treatment is presumed to be a very promising potential therapy for ED after RP. For optimization of PDE5i use, unresolved points, including the timing for the start of therapy and the appropriate dosage and duration, have to be clarified in the near future. The possibility of improved effectiveness with the combined use of vacuum devices59 and intraurethral administration of PGE149 might be important. Although this might be difficult, there are expectations for a rigorously planned, large-scale, randomized study to be carried out again, taking into account the preoperative parameters that affect postoperative EF recovery.

**Conclusion**

It has been a while since penile rehabilitation was proposed for ED after RP, though the most appropriate method for penile rehabilitation has not yet been determined. Despite the negative results of the randomized trial, penile rehabilitation using PDE5i is currently supposed to be most promising as first-line therapy for ED after RP based on many studies. It is hoped that an optimized algorithm for penile rehabilitation using PDE5i will be developed in the near future.

**Conflict of interest**

None declared.

**References**

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