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PERSPECTIVE

Sildenafil in postprostatectomy erectile dysfunction (perspective)

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Abstract
Erectile dysfunction (ED) is a common side effect to radical prostatectomies, even with nerve-sparing procedures. To ameliorate the problem so-called "penile rehabilitation" programs have been developed. The most widely used method of this is subscribing sildenafil or other PDE5-inhibitors to patients following surgery. This is based on a theory that these drugs may increase penile oxygenation and provide antiapoptotic factors (primarily NO and cGMP), thus protecting the penile tissue in a period with reduced nerve function following the surgery. Preclinical studies have confirmed the potential of sildenafil in this context and early human trials have suggested that a steady ingestion of sildenafil might protect the structural integrity of the penis. However, subsequent well-designed trials have not been able to confirm the initial findings. This fits well with sildenafil's mechanism of action because it does not actually induce erections or the production of either nitric oxide or cGMP. Rather, the drug enhances effects of an erectile response induced by neurotransmitters from the cavernous nerves. Therefore, sildenafil should no longer be offered as a sole means of penile rehabilitation. Rather, more research is needed, and clinicians need to apply a broader concept of sexual rehabilitation in postprostatectomy ED.

Introduction

Despite a limited overall survival benefit, radical prostatectomy (RP) is commonly employed for men with localized prostate cancers [1]. Unfortunately, the nerve fibers responsible for inducing erections run near the prostate gland and may be damaged by the surgery [2]. Therefore, erectile dysfunction (ED) is a common side effect. Depending on cancer growth within the gland, some men may be offered, nerve-sparing procedures in which tissue immediately surrounding the prostate is spared [3]. However, even with these nerve-sparing procedures, the erectile capacity is reduced compared to the preoperative state in the majority of patients and some suffer complete ED [4]. It has been theorized that during nerve-sparing procedures, intact nerves are affected by stretching, heating, ischemia, local inflammation, and direct trauma [5]. In this scenario the nerve function is compromised for a period of up to several years after which it may recover. Meanwhile, erections, are believed to be crucial in maintaining structural integrity of the smooth muscle in the penis through oxygen delivery [6]. Combined with a loss of growth factors, normally produced by the cavernous nerves, and the possible production of cytokines and reactive oxygen species by the now damaged nerves, this is believed to cause permanent ED through smooth muscle apoptosis and cavernosal fibrosis [7]. In fact, one small human study has used corpora cavernosa biopsies to provide histological documentation of such structural changes following RP in a sample of 19 men [8]. Based on this theory, significant efforts have been devoted to developing so-called "penile rehabilitation" programs with the purpose of improving postoperative erectile function. These aim to improve oxygenation and provide antiapoptotic factors, namely in the form of nitric oxide (NO) and its second messenger, cyclic guanosine monophosphate (cGMP) during the period of reduced nerve function.

Preclinical data

Due to its known ability to improve erections and through its mechanism of action involving precisely the NO and cGMP pathway, the phosphodiesterase 5-inhibitor (PDE5-I) sildenafil has long been seen as an ideal candidate drug for penile rehabilitation. An impressive number of preclinical studies have explored this idea, and found that administration of sildenafil may stimulate an array of growth factors

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and reduce hypoxia and oxidative stress, preserve smooth muscle, decrease fibrosis, improve electrically induced erections, and even increase the amount of myelinized nerve fibers at the area of the prior nerve crush in a rat model of cavernosal nerve damage [9–13]. Similar findings have also been made with other PDE5-inhibitors suggesting a class effect. While these results indicate a possible effect of sildenafil in penile rehabilitation, it is important to keep in mind that there are large differences between preclinical animal models and actual prostate cancer patients. Importantly, young male rats are known to have a high potential for regeneration, while this is hardly the case for middle aged men. No clinical decision should be based on animal studies; rather, these should serve as hypothesis generating studies and thus form the basis of further clinical research.

Studies in humans

In line with the preclinical data, early attempts of clinical application of sildenafil in penile rehabilitation were encouraging. In the first human study from 2004, Schwartz et al. [14] performed corpora cavernosa biopsies in 40 preoperatively potent men in conjunction with nerve-sparing RP. Participants were then randomized to either 50 or 100 mg sildenafil every other night for 6 months. Of the original 40 patients, 21 completed the study with a second corpus cavernosus biopsy at 6 months. Interestingly, there was no decline in smooth muscle content in either group and, the 100 mg Sildenafil group saw an increase in smooth muscle from a mean of 42.82% preoperatively to a mean of 56.85% postoperatively ($p < 0.05$). Four years later, Iacono and co-workers published a similar study, in which they treated 21 preoperatively potent men with 50 mg sildenafil, 3 times a week for 2 months starting 5 days after RP [15]. The authors performed penile biopsies at the time of RP and again two months later. Some degree of nerve sparing was attempted in all surgeries but according to the authors this was not always achieved. In this study, there were no changes in either smooth muscle content or penile fibrosis before and after RP. With the preservation of smooth muscle in both studies, the possible benefit of postprostatectomy sildenafil seems to be confirmed. However, the devil is in the details of the two trials and it is crucial to note that Schwartz and co-workers did not assess postoperative erectile function, while Iacono and co-workers found that just 6/21 patients reported recurrence of nightly erections at 2 months, and only 4/21 reported erections sufficient for vaginal penetration. This means that the preservation of smooth muscle cannot readily be related to functional outcomes. Furthermore, the drop-out rate of almost 50% in the Schwartz study and the lack of control groups and long-term follow up in both studies warrants caution when interpreting the results.

In 2008, the first well-designed randomized, placebo-controlled study attempting to use Sildenafil for penile rehabilitation was published by Padma-Nathan et al. [16]. Preoperatively potent men scheduled for bilateral nerve-sparing RP were randomized to nightly doses of 100 mg sildenafil, 50 mg sildenafil, or placebo for 9 months followed by an 8 week wash-out period. The study was powered to include 165 men but due to disappointing results in an interim analysis, the study was stopped early after inclusion of 125 men. Only 76 of these (61%) completed the study. Upon final analysis of the data, however, Sildenafil seemed to have had a significant effect with 14/51 regaining spontaneous erectile function in the combined sildenafil groups vs. only 1/25 in the placebo group ($p = 0.02$). The mean IIEF erectile function domain score was also higher in the sildenafil group at 13.1 ± 9.5 vs. 8.8 ± 7.0 in the placebo group (p value not given). In a subsequent publication, the potential effects of sildenafil were further highlighted as 54/76 men from the original trial had also undergone nocturnal penile tumescence measurements with the RigiScan device (Gotop Medical, Inc., St. Paul, MN, USA) [17]. Rigidity was decreased profoundly in everyone 4 weeks after surgery but it increased again during the study in the sildenafil groups, mostly in the 100 mg group. However, even in this group, the patients only achieved a mean of 36% of their base rigidity and 65% of their tip rigidity compared to baseline and the positive effects were carried primarily by the group of responders.

Taken together, these early data imply a role of sildenafil in penile rehabilitation and thus seem to confirm what clinicians deep down want to believe: that we can ameliorate a common surgical side effect by a simple postoperative prescription. But from a scientific stand point, it is necessary to be aware, that even the human data stems from two small uncontrolled trials, which relied on penile biopsies with uncertain clinical relevance and one randomized trial, which was stopped before inclusion was completed and had a drop-out rate of almost 40%. In this context, a good rule of thumb is that a dropout rate of >20% poses serious threats to validity to the study. In the end, the erections of just 14 men are a weak basis for clinical decision-making. Thankfully, further knowledge about the use of PDE5-Is in penile rehabilitation was gained from two subsequent randomized, placebo-controlled trials exploring the effects of vardenafil and tadalafil, respectively [18, 19]. Both trials were very well-designed and divided a total of 870 men (435 in each trial) into three groups receiving either nightly PDE5-Is, on-demand PDE5-Is or placebo. Neither trial was able to show any effects on spontaneous erectile function with 9 months of treatment following nerve-sparing RP. Since a possible effect of PDE5-Is in penile rehabilitation is believed to be a

class effect, this puts a serious dent into the rationale of using sildenafil in this context.

Further nails in the coffin are provided by two randomized trials comparing nightly and on-demand sildenafil. In the first of these, 100 preoperatively potent men, were randomized to either nightly or on-demand (max six tablets/month) 50 mg sildenafil for 12 months after nerve-sparing RP followed by a 1 month wash-out period [20]. In this study erections were actually better in the group who only used sildenafil sporadically compared to the nightly sildenafil group at 13 months (19.2 [SD 9.8] vs. 13.8 [SD 9.9], $p = 0.022$). However, the effect did not remain statistically significant when adjusting for nerve-sparing status and in a linear mixed-effects model, there was no significant group differences in either IIEF-EF score or on IIEF-EF recovery as a percentage of baseline score at any time point. The second study randomized 97 men with normal erectile function prior to nerve-sparing RP to either nightly 50 mg sildenafil or placebo for 12 months starting the night following surgery [21]. Both groups were allowed on-demand sildenafil. The effects on spontaneous erections were evaluated after a 1 month washout similar to previous studies. At that time, there were no differences between the groups in either IIEF-EF scores or nighttime rigidity. Contrary to these findings, a recent randomized trial ($n = 120$) has suggested a higher rate of return to potency with early on-demand sildenafil compared to treatment delayed for 3 months following surgery [22]. However, this trial has several drawbacks which limit the credibility of the findings. These include a lack of blinding and placebo control, a lack of reporting on actual sildenafil use, and the omittance of drug washout before erectile function assessment. Finally, the differences in mean postoperative IIEF-5 scores were not statistically significant between the groups, which is especially problematic as the primary outcome measure had not been clearly defined before the study (clinical trial registration: NCT01054001).

Sildenafil's mechanism of action

If we revisit the rationale behind sildenafil in penile rehabilitation with the clinical results in mind, perhaps we should not have been surprised at the lack of clear effect. In this regard, it is well-established that PDE5-Is alone do not cause spontaneous erections but rather work to enhance or prolong a weak erectile response. The reason is that PDE5-Is work by inhibiting the catalytic site of PDE5, which is an enzyme that hydrolyzes cGMP [23]. This causes intracellular cGMP accumulation in the penis and by its downstream mechanisms this will increase smooth muscle relaxation. The initial erectile response is induced primarily by NO from the cavernous nerves, while NO production from the endothelium in the penis is only subsequently induced by activation of mechanoreceptors by increased blood flow [24]. Thus, other means than PDE5-Is need to be used in men with nerve damage (temporary or permanent) to increase oxygenation and activate the NO/cGMP pathway. While some have realized this and are offering advanced algorithms for postprostatectomy treatment and rehabilitation, it is clear that a large number of centers continue to simply use PDE5-Is and wait for improvement in erectile function [25]. This may be due to tradition or a lacking knowledge of the literature, but the practice is also likely to be reinforced by PDE5-Is' ease of administration and relative lack of side effects compared to use of vacuum devices and penile injection therapy.

Conclusion

Sildenafil for penile rehabilitation seemed promising in preclinical studies and in preliminary human trials. Unfortunately, such findings are not always easy to move from bench to bedside and higher quality studies have failed to show a positive effect on spontaneous erectile function following RP. Therefore, sildenafil should no longer be offered as a sole means of penile rehabilitation. Rather, more research in this important area is needed. Logically, the main targets should be better nerve-sparing during surgery and better nerve protection afterwards. Until then, clinicians need to apply a broader concept of sexual rehabilitation in which post-prostatectomy ED is treated aggressively using the whole arsenal of erectogenic aids, and where the issue is discussed with both patients and their partners. Theoretically this may provide penile oxygenation and NO/cGMP activation, which will protect the penile tissue and likely it will defer the psychological and relationship effects of long-lasting ED. In any case, the days of simply offering penile rehabilitation by prescribing a blue pill are over.

Compliance with ethical standards

Conflict of interest MF is a speaker for Astellas Pharma and Ferring Pharmaceuticals and an advisory board member for Astellas Pharma. PBØ is a speaker for Astellas Pharma, Ferring Pharmaceuticals, and Ipsen, and an advisory board member for Astellas Pharma and Ipsen. CFSJ declare that he has no conflict of interest.

References

1. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med. 2016;375:1415.

2. Walz J, Burnett AL, Costello AJ, Eastham JA, Graefen M, Guillonneau B, et al. A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol. 2010;57:179.
3. Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. J Urol. 1982;128:492.
4. Fode M, Frey A, Jakobsen H, Sonksen J. Erectile function after radical prostatectomy: do patients return to baseline? Scand J Urol. 2016;50:160.
5. Burnett AL. Rationale for cavernous nerve restorative therapy to preserve erectile function after radical prostatectomy. Urology. 2003;61:491.
6. Kim N, Vardi Y, Padma-Nathan H, Daley J, Goldstein I, Saenz DT,I. Oxygen tension regulates the nitric oxide pathway. Physiological role in penile erection. J Clin Invest. 1993;91:437.
7. Hatzimouratidis K, Burnett AL, Hatzichristou D, McCullough AR, Montorsi F, Mulhall JP. Phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction: a critical analysis of the basic science rationale and clinical application. Eur Urol. 2009;55:334.
8. Iacono F, Giannella R, Somma P, Manno G, Fusco F, Mirone V. Histological alterations in cavernous tissue after radical prostatectomy. J Urol. 2005;173:1673.
9. Vignozzi L, Morelli A, Filippi S, Vannelli GB, Mungai S, Marini M, et al. Effect of sildenafil administration on penile hypoxia induced by cavernous neurotomy in the rat. Int J Impot Res. 2008;20:60.
10. Mulhall JP, Muller A, Donohue JF, Mullerad M, Kobylarz K, Paduch DA, et al. The functional and structural consequences of cavernous nerve injury are ameliorated by sildenafil citrate. J Sex Med. 2008;5:1126.
11. Kovanecz I, Rambhatla A, Ferrini M, Vernet D, Sanchez S, Rajfer J, et al. Long-term continuous sildenafil treatment ameliorates corporal veno-occlusive dysfunction (CVOD) induced by cavernosal nerve resection in rats. Int J Impot Res. 2008;20:202.
12. Ozden E, Ozturk B, Kosan M, Tezel GG, Aki FT, Gur S, et al. Effect of sildenafil citrate on penile weight and physiology of cavernous smooth muscle in a post-radical prostatectomy model of erectile dysfunction in rats. Urology. 2011;77:761.
13. Sirad F, Hlaing S, Kovanecz I, Artaza JN, Garcia LA, Rajfer J, et al. Sildenafil promotes smooth muscle preservation and ameliorates fibrosis through modulation of extracellular matrix and tissue growth factor gene expression after bilateral cavernosal nerve resection in the rat. J Sex Med. 2011;8:1048.
14. Schwartz EJ, Wong P, Graydon RJ. Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. J Urol. 2004;171:771.
15. Iacono F, Prezioso D, Somma P, Chierchia S, Galasso R, Micheli P. Histopathologically proven prevention of post-prostatectomy cavernosal fibrosis with sildenafil. Urol Int. 2008; 80:249.
16. Padma-Nathan H, McCullough AR, Levine LA, Lipshultz LI, Siegel R, Montorsi F, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res. 2008;20:479.
17. McCullough AR, Levine LA, Padma-Nathan H. Return of nocturnal erections and erectile function after bilateral nerve-sparing radical prostatectomy in men treated nightly with sildenafil citrate: subanalysis of a longitudinal randomized double-blind placebo-controlled trial. J Sex Med. 2008;5:476.
18. Montorsi F, Brock G, Lee J, Shapiro J, Van PH, Graefen M, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol. 2008;54:924.
19. Montorsi F, Brock G, Stolzenburg JU, Mulhall J, Moncada I, Patel HR, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). Eur Urol. 2014;65:587.
20. Pavlovich CP, Levinson AW, Su LM, Mettee LZ, Feng Z, Bivalacqua TJ, et al. Nightly vs on-demand sildenafil for penile rehabilitation after minimally invasive nerve-sparing radical prostatectomy: results of a randomized double-blind trial with placebo. BJU Int. 2013;112:844.
21. Kim DJ, Hawksworth DJ, Hurwitz LM, Cullen J, Rosner IL, Lue TF, et al. A prospective, randomized, placebo-controlled trial of on-demand vs. nightly sildenafil citrate as assessed by Rigiscan and the international index of erectile function. Andrology. 2016;4:27.
22. Jo JK, Jeong SJ, Oh JJ, Lee SW, Lee S, Hong SK, et al. Effect of starting penile rehabilitation with sildenafil immediately after robot-assisted laparoscopic radical prostatectomy on erectile function recovery: a prospective randomized trial. J Urol. 2018; 199:1600.
23. Francis SH, Corbin JD. Sildenafil: efficacy, safety, tolerability and mechanism of action in treating erectile dysfunction. Expert Opin Drug Metab Toxicol. 2005;1:283.
24. Hurt KJ, Musicki B, Palese MA, Crone JK, Becker RE, Moriarity JL, et al. Akt-dependent phosphorylation of endothelial nitric-oxide synthase mediates penile erection. Proc Natl Acad Sci USA. 2002;99:4061.
25. Tal R, Teloken P, Mulhall JP. Erectile function rehabilitation after radical prostatectomy: practice patterns among AUA members. J Sex Med. 2011;8:2370.