Return to Pre-treatment Status After RP: Myth or Reality?

Ege Can Serefoglu, MD, FECSM

Bagcilar Training & Research Hospital, Istanbul, Turkey
It is a Myth...
Financial and Other Disclosures

- Off-label use of drugs, devices, or other agents: None or FILL IN HERE; including your local regulatory agency, such as FDA, EMA, etc.

- Data from IRB-approved human research is presented [or state: “is not”]

<table>
<thead>
<tr>
<th>I have the following financial interests or relationships to disclose:</th>
<th>Disclosure code</th>
</tr>
</thead>
<tbody>
<tr>
<td>No financial relationships</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Return to Pre-treatment Status After RP: Myth or Reality?

- Incidence & Predictors of Post-RP ED
- Pathophysiology of Post-RP ED
- Penile Rehabilitation
  - On-demand / Daily PDE-5 inhibitors
  - Intracavernosal Injections
  - VED
Return to Pre-treatment Status After RP: Myth or Reality?

- Incidence & Predictors of Post-RP ED
- Pathophysiology of Post-RP ED
- Penile Rehabilitation
  - On-demand / Daily PDE-5 inhibitors
  - Intracavernosal Injections
  - VED
The incidence of post-RP ED range between 15-95%\textsuperscript{1}

Meta-analysis of RARP trials\textsuperscript{2}
- 12 month – 10-46% ED
- 24 month – 6-37% ED

Post-op EF recovery:
- Majority within 2 yr
- Fails to achieve baseline

1. Mulhall JP. J Urol 2009
Predictors of Post-RP ED

- Models developed for prediction of post-RP ED based on individual patient characteristics
  - Based on data of men completing 2 years follow-up (n = 1027)
Predictors of Post-RP ED

Factors which influence postoperative EF:

- nerve-sparing status,
- patient age,
- preoperative EF,
- Comorbidities

- surgical technique (RARP?)
- Surgical tools (Cautery?)
- surgeon experience

Return to Pre-treatment Status After RP: Myth or Reality?

- Incidence & Predictors of Post-RP ED
- Pathophysiology of Post-RP ED
- Penile Rehabilitation
  - On-demand / Daily PDE-5 inhibitors
  - Intracavernosal Injections
  - VED
Pathophysiology of post-RP ED
Pathophysiology of post-RP ED

Hatzimouratidis et al Eur Urol 2009
Post-RP Penile Histologic Changes

Pre-RP

Post-RP

reduced cavernosal smooth muscle tissue (2nd postoperative month)

Return to Pre-treatment Status After RP: Myth or Reality?

- Incidence & Predictors of Post-RP ED
- Pathophysiology of Post-RP ED
- Penile Rehabilitation
  - On-demand / Daily PDE-5 inhibitors
  - Intracavernosal Injections
  - VED
Penile rehabilitation

Defined as the use of any intervention or combination with the goal

- to achieve erections sufficient for satisfactory sexual intercourses,
- to return to preoperative EF levels

The concept of penile rehabilitation is based on the implementation of therapeutic protocols aimed at

- improving cavernosal oxygenation,
- preserving endothelial structure,
- preventing smooth muscle structural changes

during erections the penis oxygenation rises from 35-40 → 75-100 mmHg

Thus, oxygenation is preserved as long as men obtain erections regularly.
1997: Montorsi et al. Early postoperative **alprostadil injections** increases the recovery of spontaneous erections

1998: **Viagra®** is the first PDE5I approved by the FDA for the treatment of erectile dysfunction

2003: Padma-Nathan et al. A randomized, placebo-controlled study - **nightly sildenafil** for the return of normal erections

2004: Schwartz et al. uncontrolled trial **sildenafil** preserves (or even increases) intracorporal smooth muscle content

2005: Mulhall describes an erectogenic pharmacotherapy regimen **combining PDE5I with intracavernous injections** and shows benefit of this approach in a nonrandomized trial
2008: Montorsi et al. fail to show the effectiveness of **daily vardenafil** in a large double-blind prospective randomized trial, compared with on-demand use and placebo

2013: Pavlovich et al. fail to show the effectiveness of **daily sildenafil** in a large double-blind prospective randomized trial, compared with on-demand use and placebo

2014: Montorsi et al. fail to show the effectiveness of **daily tadalafil** in a large double-blind prospective randomized trial, compared with on-demand use and placebo
Penile rehabilitation

Available Tx
- On-demand / Daily PDE-5 inhibitors
- Intracavernosal Injections
- Vacuum Erection Devices (VED)
PDE-5 inhibitors

- the most commonly performed type of penile rehabilitation
- up to 87% of the surgeons adopted this treatment strategy
- clinical studies reported conflicting results
- preclinical data support the beneficial effects of these molecules

PDE5-I after nerve damage in Rats

Benefits

- ↑ cavernosal pressure after injection or electrical stimulation
- ↑ smooth muscle
- ↑ neuroregeneration
- ↓ fibrosis
- ↓ degeneration of nerves

Possible mechanisms

- cGMP and NO activation
- Hypoxia ↓
- Endothelial protection
- Anti-apoptotic and anti-fibrotic factors
- Oxidative stress ↓
- cell proliferation ↑
- Nerve protection

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Design</th>
<th>Population</th>
<th>Drug</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montorsi et al. 2008</td>
<td>Multicenter double-blind double-dummy randomized controlled trial</td>
<td>A total of 628 men, aged 18-64 yrs, were randomized to treatment. Study design consisted of a 9-mo double-blind treatment period, a 2-mo single-blind washout period, and an optional 2-mo open-label period. Patients received placebo, nightly vardenafil 10 mg, or on-demand vardenafil.</td>
<td>Vardenafil</td>
<td>11 months</td>
<td>• On-demand vardenafil treatment resulted in significantly greater IIEF-EF scores and better SEP3 response rates than placebo over the entire double-blind treatment period. • No statistically significant differences were observed among treatment groups in the proportion of patients with an IIEF-EF score of ≥22 or in SEP3 success rates after the washout period.</td>
</tr>
<tr>
<td>Aydogdu et al. 2011</td>
<td>Randomized controlled trial</td>
<td>A total of 65 patients underwent bilateral nerve sparing radical prostatectomy. Patients were randomized to control without rehabilitation (group 1) or tadalafil 20 mg 3 times a week for 6 months rehabilitation group (group 2).</td>
<td>Tadalafil</td>
<td>12 months</td>
<td>• In group 1 there was significant decrease in penile measurements at month 3 compared to preoperative measurements. • At the 12-month follow-up, there were no differences between stretched penile length in the two groups and no significant differences in erectile function between the two groups.</td>
</tr>
<tr>
<td>Mulhall et al. 2013</td>
<td>Double blind, placebo-controlled randomized study</td>
<td>298 patients aged 18 to 70 years with a history of erectile dysfunction of 6 months or more after bilateral nerve-sparing radical prostatectomy. Patients were randomized to 100 or 200 mg of avanafil or placebo on demand for 12 weeks.</td>
<td>Avanafil</td>
<td>12 weeks</td>
<td>• After 12 weeks there were significantly greater increases in SEP2 and SEP3 and change in mean IIEF-EF domain score with 100 and 200 mg avanafil vs. placebo (P&lt;0.01). • Following dosing with avanafil, 36.4% (28 of 77) of sexual attempts (SEP3) at 15 minutes or less were successful vs. 4.5% (2 of 44) for placebo (P&lt;0.01).</td>
</tr>
<tr>
<td>First author and year</td>
<td>Design</td>
<td>Population</td>
<td>Drug</td>
<td>Follow-up</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pavlovich et al. 2013</td>
<td>Single-institution, double-blind, randomized controlled study</td>
<td>100 preoperatively potent patients with clinically localized prostate cancer treated with nerve-sparing robot-assisted radical prostatectomy. Patients were randomized to either nightly sildenafil and on-demand placebo (nightly sildenafil group), or on-demand sildenafil and nightly placebo (on-demand sildenafil group; maximum on-demand dose six tablets/month) for 12 months. Patients then underwent a 1-month washout period</td>
<td>Sildenafil</td>
<td>13 months</td>
<td>• No significant differences were observed between treatments (nightly vs. on-demand sildenafil) in terms of postoperative IIEF-EF and return to baseline IIEF</td>
</tr>
<tr>
<td>Montorsi et al. 2014</td>
<td>Randomized double-blind double-dummy placebo controlled trial</td>
<td>Men ≤68 year of age with prostate cancer (Gleason ≤7) and normal preoperative EF who underwent nerve-sparing RP at 50 centers from nine European countries and Canada (n=423) A 1:1:1 randomization to 9 months of treatment with tadalafil 5 mg once daily, tadalafil 20 mg on demand, or placebo followed by a 6-week drug-free washout and 3-month open-label tadalafil once daily (all patients)</td>
<td>Tadalafil</td>
<td>13.5 months</td>
<td>• 20.9%, 16.9%, and 19.1% of patients in the tadalafil once daily, on demand, and placebo groups, respectively, achieved IIEF EF scores ≥22 after drug-free washout. • At the end of double-blind treatment, mean IIEF-EF score improvement significantly exceeded the minimally clinically important difference (MCID: ΔIIEF-EF ≥4) in both tadalafil groups. • For SEP-3 (MCID ≥23%), this was the case for tadalafil once daily only. • At the end of double-blind treatment, penile length loss was significantly reduced versus placebo in the tadalafil once daily group only (P=0.03).</td>
</tr>
<tr>
<td>First author and year</td>
<td>Design</td>
<td>Population</td>
<td>Drug</td>
<td>Follow-up</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------</td>
<td>-----------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pavlovich et al. 2013</td>
<td>Single-institution, double-blind, randomized controlled study</td>
<td>100 preoperatively potent patients with clinically localized prostate cancer treated with nerve-sparing robot-assisted radical prostatectomy. Patients were randomized to either nightly sildenafil and on-demand placebo (nightly sildenafil group), or on-demand sildenafil and nightly placebo (on-demand sildenafil group; maximum on-demand dose six tablets/month) for 12 months. Patients then underwent a 1-month washout period.</td>
<td>Sildenafil</td>
<td>13 months</td>
<td>• No significant differences were observed between treatments (nightly vs. on-demand sildenafil) in terms of postoperative IIEF-EF and return to baseline IIEF.</td>
</tr>
</tbody>
</table>
| Montorsi et al. 2014  | Randomized double-blind double-dummy placebo controlled trial | Men ≤68 year of age with prostate cancer (Gleason ≤7) and normal preoperative EF who underwent nerve-sparing RP at 50 centers from nine European countries and Canada (n=423). A 1:1:1 randomization to 9 months of treatment with tadalafil 5 mg once daily, tadalafil 20 mg on demand, or placebo followed by a 6-week drug-free washout and 3-month open-label tadalafil once daily (all patients). | Tadalafil | 13.5 months | • 20.9%, 16.9%, and 19.1% of patients in the tadalafil once daily, on demand, and placebo groups, respectively, achieved IIEF EF scores ≥22 after drug-free washout.  
• At the end of double-blind treatment, mean IIEF-EF score improvement significantly exceeded the minimally clinically important difference (MCID: ΔIIEF-EF ≥4) in both tadalafil groups.  
• For SEP-3 (MCID ≥23%), this was the case for tadalafil once daily only.  
• At the end of double-blind treatment, penile length loss was significantly reduced versus placebo in the tadalafil once daily group only (P=0.03). |

MCID, minimal clinically important difference; SEP, Sexual Encounter Profile; IIEF-EF, International Index of Erectile Function—Erectile Function domain.
Vardenafil – Montorsi 2008

- A randomised, double-blind, double-dummy, multicentre, parallel group study conducted at 87 centres across Europe, Canada, South Africa, and the United States.

- 628 men with normal preoperative EF

- After nerve sparing RP
  - Vardenafil daily
  - On-demand
  - Placebo

- 9-mo double-blind treatment period → 2-mo single-blind washout period, and an optional 2-mo open-label period.

*Primary outcome IIEF≥22 after washout

Take Home Points:

1. Biggest RCT
2. NO difference after washout
3. NO benefit on subsequent on-demand response
• Randomised, double-blind, double-dummy, placebo-controlled trial in men ≤ 68 yr of age with prostateca (Gleason ≤ 7) and normal preoperative EF
• 50 centres from nine European countries and Canada.

• 423 men after nerve sparing RP
  • Tadalafil 5 mg daily
  • Tadalafil 20 mg prn
  • Placebo

• 9 mo double-blind treatment period → 6 weeks washout → 12 weeks open label tadalafil 5 mg

• *Primary outcome IIEF≥22 after washout

Take Home Points:

1. **NO** difference after washout
2. **NO** benefit on subsequent tx response
Washout

Measurements of penile length as a surrogate measure of cavernous tissue integrity

Daily tadalafil preserves penile length (4.1 mm better than placebo)
PDE5-inhibitors conclusion

- PDE5-I is an excellent tx in post-RP ED
  - Daily and on-demand are equal

- PDE5-I offers limited tissue protection

- PDE5-I has no effect on spontaneous EF
Other methods

- Injection
- Muse
- Vacuum devices
Intracavernosal Injections

- **Alprostadil injections** after nerve-sparing surgery

- 30 patients - nerve randomized to
  - injections 3 times per week for 12 weeks
  - observation

- 12 patients (80%) completed the entire treatment schedule

- 67% in treatment group (and 20% in control group) reported recovery of "spontaneous erections" $(p < 0.01)$

Traction Therapy / VED

- Post-RP traction therapy preserves and/or improves penile length\(^1\)
- Early initiation of VED post-prostatectomy improves early sexual function\(^2\)
- No washout periods or assessment without devices

Recommendations after RP?

- Encourage sexual activity
  - Long periods without sexual activity may cause ED
  - Long periods without sexual activity will influence confidence and relationships

- Use erectogenic treatments
  - Theory behind “penile rehabilitation” demands erections
  - PDE5Is work (at least when the patients use them)

- Focus on whole person
  - Incontinence
  - Neglected sexual side effects (EjD, loss of libido etc)
  - Changes in the patient’s life situation
  - Don’t forget the partner..!
1. Multiple causes of iatrogenic ED

2. Loss of erections may lead to changes in collagen / smooth muscle ratio and result in permanent ED – prevents response to erectogenic agents

3. Encourage sexual activity - Long periods without sexual activity will influence confidence and relationships

4. Goals of penile rehabilitation are to prevent loss of penile functional tissue and improve responsiveness to agents

5. Optimal agent for rehab is unclear
Conclusion

6. No clear benefit using PDE5I for permanent rehabilitation (Viagra, Levitra, Cialis)
   • Improves erections while taking..!
   • Lack of evidence for prevention of permanent loss of function / restoration of function

6. Injection therapies may often be required

7. Vacuum or penile traction helps maintain / improve length

8. Focus on whole person
   - Incontinence
   - Neglected sexual side effects
   - Changes in the patient’s life situation
   - Don’t forget the partner..!
Thank you...