

**Which form of andrological rehabilitation  
in patients**

**post radical prostatectomy?**

**DRUG MANAGEMENT**



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Despite the recent refinements in the anatomic approach to radical prostatectomy, erectile dysfunction (ED) is a **common and significant side effect** in men treated for prostate cancer.

In the literature, the ED rates in this pool of patients after surgery are reported

**10 - 90%**

(Siegel, 2001)

## ED post radical prostatectomy

In non-selected prostatectomy patients, **Pontes (1986)** reported ED in **54%**, **Kao (2000)** in **88.4%**, and **Fischetti (2001)** in **47%**.

In bilateral NSRRP, **Gralnek (2000)** and **Noldus (2001)** independently found ED in **50%** of the cases.

**Vela (1997)**, reevaluating previously potent subjects, reported ED in **90%** of non NSRRP and in **10%** of NSRRP.

On the contrary, **Stanford (2000)**, examining a wide population of 1291 previously potent patients 1,5 yrs. after surgery, reported ED in: **65.6%** of non nerve sparing RRP, **58.6%** of monolateral NSRRP, and **56.0%** of bilateral NSRRP.

## ED post radical prostatectomy

**Miyao (2001)**, in a study of sexual function in 40 patients submitted to bilateral NSRRP, using NPT test and pre- and post-operative questionnaires, reported a recovery after surgery of the erectile function in **49%** of them 3 yrs. later and in **79%** 5 yrs. later, and the regaining of the penetration ability in **36%** 3 yrs. later and in **57%** 5 yrs. later.

**The recovery of erectile function depends upon the preoperative NPT values and the recovery of sexual intercourses (penetration ability) depends upon the age of the patient.**

The causes of post-RP ED are not yet perfectly well known.

In these cases ED could be attributed to neurogenic factors or to vascular lesions or both.

About **vascular dysfunction, an arteriogenic factor** has been proposed by many investigators (Zalefsky, 1998; Vela, 1997; Mulhall, 1996; Polascik, 1995; Aboscif, 1994), according to Droupy (1999) due to a damage of the accessory pudendal arteries. Anyway, more recently **a damage of the corporo-occlusive mechanism** has been proposed, too. Nevertheless De Luca (1996) refers a prevalence of post-radical prostatectomy CVOD in 5 % of cases only.

The interval of time after surgery is significantly associated with the incidence of **venous leakage**:

14% < at 4months vs 35% > at 9 months

It appears that the prognosis for return of erection is worst when venous leakage is present.

(Mulhall, 2002)

neurovascular damage

↓  
⇓ O<sub>2</sub>

↑↑ collagene production (corpora fibrosis)

↓  
veno-occlusive disfunction

(Moreland, 1998)

## **IMMEDIATE OR LATE DRUG THERAPY?**

**According to the current opinion, to avoid penile fibrosis, rehabilitation should be soon started.**

**In the rats submitted to erectile nerves surgical trauma, high O<sub>2</sub> tension was shown to promote the synthesis of a growth hormone able to stimulate the development of nervous fibers containing NO synthetase. This seems to be one of the main factors to recover erectile function.**

**(Jung, 1998)**

By means of morphometric evaluations, **Fraiman (1999)** showed, in patients submitted to RRP, even in cases of NSRRP, significant post-operative penile anatomical changes, i.e.: **8% shortening in penile length and 9% reduction in circumference.**

In addition, men experiencing ED following RRP show higher libido than in other forms of ED, in contrast to the severe physical damage.

Penile morphometric changes are prevalently observed **in the first 4-8 months** after surgery and could be attributed to hypoxia-induced fibrosis or to denervation-induced smooth muscle hypotrophy in the corpora.

## Andrological rehabilitation post-radical prostatectomy

Prior to oral treatments, management of ED after radical prostatectomy was focused on

*three main therapies* :

vacuum constriction devices

intracavernosal injections

prosthetic penile implants

(Hall, 1995)

## **VACUUM DEVICE** **(without a constriction band)**

From a physiologic point of view, it means a **passive forced tissue oxygenation.**

Its action is based on a **stretching effect**, opposing to fibrosis development and penile shortening.

Colombo (2000) suggests to use the Vacuum Device just one month after surgery, **three times a week**, rejecting the hypothesis of VD-induced fibrosis.

## **VACUUM DEVICE** **(without constriction band)**

**It could be associated with oral treatment by sildenafil (3 times/week, 50-100 mg), obtaining a synergic effect. Alternatively, it could be combined with 20%-papaverin gel glandular application.**

**(Colombo, 2002)**

## **VACUUM DEVICE vs ICI PGE<sub>1</sub>:**

**Patients' compliance of both these forms of rehabilitation results not statistically different.**

**(Carson, 1996)**

## ICI after radical prostatectomy

In the last decades, patients undergoing pelvic surgery, often later unavoidably affected by ED, used to be treated with intracavernous injection of vasoactive drugs (ICI). In fact the latter was the only treatment able to guarantee them adequate erections. So, ICIs were then used as ***“symptomatic treatment”***.

Subsequently, some subjects chronically treated by ICIs were shown to recover erection partially. From the consequent need to reduce drug's doses in these patients, emerged the idea of using ICIs as a form of rehabilitation, so passing from a “symptomatic” to a ***“causal treatment”***.

## ICI after radical prostatectomy

- Nowadays, ICI therapy are currently considered a satisfactory rehabilitation therapy for RP patients suffering from ED.
- ICI therapy offers the best improvement in induced and in natural erection.
- ICI therapy shows **95% success rate** in induced erections and **near 10% improvement in natural erections.**

(Rodriguez Vela, 1997; Sharlip, 1997; Colpi, 2002)

## ICI after radical prostatectomy

On the contrary, **Montorsi (1997)** claimed that ICI therapy in the immediate RRP post-operative period induces recovery of spontaneous erections in **67%** of the cases vs **20 %** of the cases treated later. He suggests a treatment based on **3 ICIs a week, 12 weeks at least.**

## **ICI in radical prostatectomy**

**A single ICI a week may be insufficient in a ED rehabilitation program for RP patients.**

**(Montorsi, 2002)**

**In order to rehabilitate the cavernous smooth muscle, drug doses able to induce a firm erection are not needed.**

**In fact, better tissue oxygenation is achieved during the pre-firm erection than during full rigidity.**

**(Colombo, 2002)**

## ICI after radical prostatectomy

ICI treatment is generally performed using **alprostadil**, a synthetic analogue of PGE<sub>1</sub>, starting with low doses (3μg), due to RRP patients' hyperresponsivity.

**Drug cocktails** (papaverine, phentolamine etc.) are used in non responsive high-dose PGE<sub>1</sub> cases, to minimize adverse effects.

## **ICI after radical prostatectomy**

**Acceptability and compliance with ICI of PGE<sub>1</sub> often limit the use.**

**Management of ED after RRP must start with the preoperative encouragement to use ICI.**

**(Lebret, 1999)**

## ICI rehabilitation in radical prostatectomy

Even if long term ICI therapy does not change NPT parameters in organogenic ED (**Maniam, 2001**), the response achieved in terms of spontaneous erections increases from **37 to 88%**

(Broch, 2001)

## ICI rehabilitation in radical prostatectomy

### PGE<sub>1</sub> ICI COMPLICATIONS

<b>Pain</b>	<b>30%</b>
<b>Penile nodule</b>	<b>13%</b>
<b>Prolonged penile erection</b>	<b>6%</b>

**Drop-out: 28-67%**

(Montorsi, 2002)

## Oral therapy after radical prostatectomy

Sildenafil was the first drug used orally with a demonstrated clinical efficacy in the rehabilitation of ED RRP patients.

### Factors influencing sildenafil response:

- degree of nerve sparing
- baseline postoperative ED
- age
- pathological stage of carcinoma

(Lowentritt, 1999; Feng, 2000)

## Sildenafil citrate

The degree of neurovascular bundle preservation in radical retropubic prostatectomy is the fundamental factor in penile erections recovery.

Resection of one neurovascular bundle reduce the chance of recovery to **25%** compared to preserving both nerves (**76%** pts <60 yrs.; **50%** pts >60 yrs.)

(Rabbani, 2000)

## Sildenafil citrate

**Integrity of neurovascular bundles is necessary.**

**In fact, sildenafil effects are correlate prevalently to NO release from NANC- nervous terminations.**

**Only elevate doses of sildenafil can utilize the reaction even from endothelial NO.**

**Doses: 50-100 mg three times a week, at least**

(Hong, 1999)

## Sildenafil citrate

**Sildenafil in ED following NSRP improves erections in >50% patients, and the ability for intercourse in 40% patients.**

**Orgasmic function and intercourse satisfaction also result ameliorated according to IIEF questionnaires.**

**(Lowentritt, 1999)**

## Sildenafil citrate

**Hong (1999)**, examining pre- and post-surgery erectile function in RP patients with EDITS questionnaires, reports a significant increase in the treatment satisfaction rate with increasing time from surgery: **between 0 - 6 months after surgery the treatment satisfaction rate is 26%, peaking at 60% between 18 months - 2 years**

His conclusions are that the response to sildenafil appears to be dependent upon the interval between RRP and the start of sildenafil, so early non responders to sildenafil should not be disheartened, as they will more likely respond later.

## Sildenafil citrate

Therefore, sildenafil administration results to be not effective immediately after surgery: on the contrary, it shows its **efficacy following the resolution from surgical “stupor” affecting penile nerves.**

(Mc Cullough, 2001)

Sildenafil citrate is ineffective during the first **9 months after surgery.**

(Zagaja, 2000)

## Sildenafil citrate

Sildenafil rehabilitation is based on suppression of TGF-beta<sub>1</sub> mediated - collagen synthesis in the cavernosal smooth muscle, preventing the vascular and cavernous fibrosis responsible of the CVOD and the arterial damage.

**Nehra (2002)** and some other investigators suggest to associate **sildenafil with PGE<sub>1</sub>[MUSE]**, so acting on both the two second messengers involved in smooth muscle corporeal relaxation (cAMP and cGMP). Nevertheless, this association, ideally more profitable in selected scarcely responsive cases, did not show clinically the expected advantages.

## Sildenafil citrate

**Sildenafil might be an effective treatment even for patients submitted to bilateral nerve grafting during RRP (using sural nerve graft interposition).**

**Kim (2001) reports a positive response in 43% of these patients.**

## **Oral therapy after radical prostatectomy**

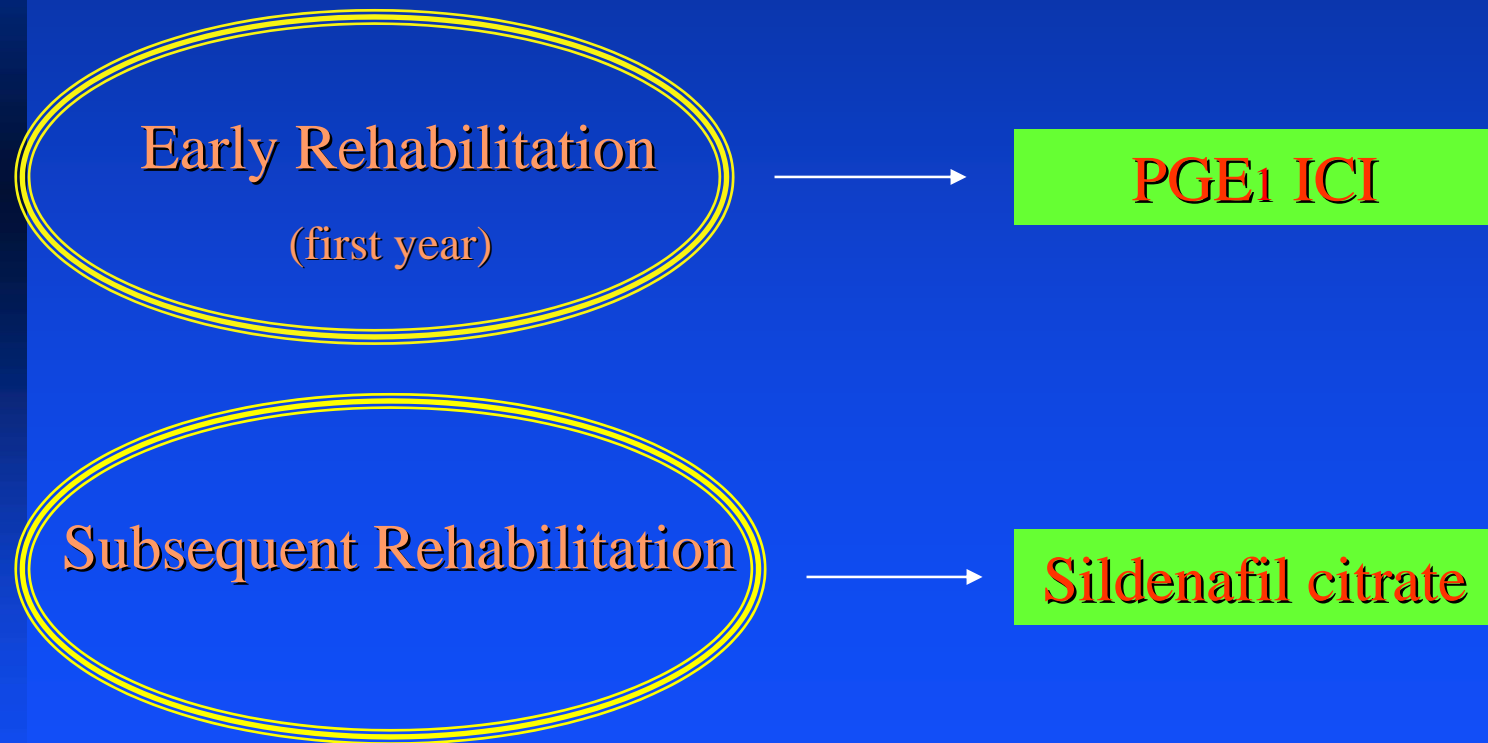
### **Apomorphine**

**Has apomorphine a role in the ED rehabilitation of RRP patients?**

**We have not been able to find any data in the literature about this topic.**

# Algorithm in Radical Prostatectomy ED Rehabilitation

## SEQUENTIAL TREATMENTS



## Radical Prostatectomy DE Rehabilitation

Penetration ability in patients operated on monolateral NSRRP following two year rehabilitation

ICI PGE<sub>1</sub>

44%

Sildenafil citrate

17%

Sildenafil citrate + VD

39%

(Colombo, 2002)

## CONCLUSIONS

**Corporeal rehabilitation is always advisable.**

**It is a long, exacting and hard procedure.**

**It must be initiated early: one month after surgery (ICI  
3 times weekly, for 1 year).**

**It must be maintained for some other months by  
means of sildenafil (50-100 mg, 3 times a week),  
stopping ICIs due to their increased risk of inducing  
penile fibrosis.**

**New oral drugs (like tadalafil and vardenafil) seem at  
the moment promising agents for the second  
rehabilitation phase.**

**Dopaminergic receptors have been identified even in  
the cavernous tissue: therefore, also studies on  
apomorphine might be useful.**