

## IATROGENIC ERECTILE DYSFUNCTION AFTER PELVIC SURGERY: PROSTATECTOMY, COLONIC AND RECTAL SURGERY

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**IATROGENIC ERECTILE DYSFUNCTION AFTER PELVIC SURGERY: PROSTATECTOMY, COLONIC AND RECTAL SURGERY (ABSTRACT):** Radical pelvic surgery: radical prostatectomy, colonic and rectal surgery are iatrogenic causes of erectile dysfunction with major impact on health-related quality of life. The major cause of erectile dysfunction in such surgical procedures is cavernous nerve injury that leads to apoptosis of cavernous smooth muscle, fibrosis and venoocclusive disease. After radical nerve-sparing prostatectomy up to 50 % of patients may develop erectile dysfunction and recover rate varies from 16% to 86 % in 6-12 month. The prevalence of erectile dysfunction after rectal surgery varies largely according to the technique used, nerve dissection, associated irradiation and chemotherapy from 33 % to 95 %. Laparoscopic and robotic-assisted surgery allows a better autonomic nerve preservation and a better postoperative sexual function. Rehabilitation programs in patients with iatrogenic erectile dysfunction must start as soon as possible in order to provide blood supply, good oxygenation and to prevent smooth muscle loss and fibrosis. Best candidates for this program are young patients with normal sexual function before surgery. First line therapy in rehabilitation programs are phosphodiesterase type 5 inhibitors, followed by intracavernosal erectogenic drugs injections and vacuum constriction devices. Rehabilitation programs are efficient in 14%-81% of patients with bilateral nerve-sparing prostatectomy and in 43%-93% of patients following robotic-assisted laparoscopic surgery.

**KEY WORDS:** RADICAL PROSTATECTOMY, PROCTOCOLECTOMY, ERECTILE DYSFUNCTION, REHABILITATION IN IATROGENIC ERECTILE DYSFUNCTION.

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### INTRODUCTION

Radical pelvic surgery is an important cause of iatrogenic erectile dysfunction [1]. Most data in literature deal with erectile dysfunction after radical prostatectomy, but data on sexual consequences of colonic and rectal surgery are also available.

Radical prostatectomy remains standard therapy for localized prostate cancer [2]. Erectile dysfunction is one of the most important issue following radical prostatectomy with significant negative impact on health-related quality of life [3,4]. Occurrence of sexual dysfunction and its recovery after radical prostatectomy depends of surgical procedure – the ability to perform a nerve sparing surgery and previous sexual function of the patients [5].

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## **PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION AFTER PELVIC SURGERY**

Both experimental and clinical data prove that cavernous nerve injury during pelvic surgery is responsible for erectile dysfunction. After experimental ablation of cavernous nerve, smooth muscle apoptosis begins after 1 day and rapidly induces fibrosis and pelvic atrophy [6].

Cavernous nerve injury induces over expression of pro-apoptotic factors with smooth muscle of cavernous tissue loss and profibrotic factors that produces increased collagen content within corpora cavernosa and venoocclusive dysfunction [2,3]. After radical prostatectomy there is a rapid decline in nocturnal erection and cavernous hypoxia which also contributes to cavernous hypoxia, muscle apoptosis, venous leak and erectile dysfunction [4,7,8]. Lack of preservation of accessory pudendal artery increases the risk for cavernous tissue hypoxia.

Bilateral cavernous nerve injury results in oxidative stress-associated tissue damage [9]. The mechanisms that are directly involved in erection. Expression of smooth muscle actin and caveolin-1 a protein localized at the surface of smooth muscle cells and connected with nitric oxide synthase and nitric oxide generation are decreased after unilateral or bilateral cavernous nerve injury [1].

## **ERECTILE DYSFUNCTION AFTER RADICAL PROSTATECTOMY**

The effects of prostatic radical surgery essentially depends of the ability of cavernosal nerve preservation. Data on the iatrogenic erectile dysfunction after radical prostatectomy and spontaneous or rehabilitation aided recovery are different according to the technique used to perform the operation. Khera [10] reported an impressive prevalence of erectile dysfunction after radical prostatectomy up to 80 % of cases.

After nerve – sparing radical prostatectomy 50 % of patients may develop erectile dysfunction [11]. Other reports are more optimistic: bilateral nerve-sparing prostatectomy may preserve sexual function in 88.1 % of patients, with spontaneous rehabilitation of sexuality in 83 % after 1 year and 95.1 % after 2 years [12].

In radical prostatectomy erectile function may recover in 16%-40%-86 % of cases, and the time for recovery varies between 6-12-24 month [4,7,8]. After bilateral nerve-sparing prostatectomy erectile function may return to normal after 6-18 month [5].

Iatrogenic erectile dysfunction may occur depending of the stage of the disease. After radical prostatectomy and/or cysto-prostatectomy erectile function may be preserved in up to 74 % on patients, being initially reduced but with a trend to recovery in the first 2 years. Recovery of sexual function may be seen in 93 % of patients in the first stage of the disease, in 73 % in stage A2, 72 % in stage B1 and 56 % in stage B [13].

Irradiation for prostate cancer has a negative impact on sexual function: 45 % of irradiated patients have sexual dysfunction after 9-18 month and 77 % after 5 years [14].

Two methods may predict sexual function after prostatectomy: assessment of nocturnal spontaneous erection and Doppler duplex penile ultrasonography.

Assessment of nocturnal penile erections with Rigiscan device proves after nerve sparing prostatectomy the presence of nocturnal penile erection in 95 % of patients with normal nocturnal erection prior surgery and a rigidity of 70 % for more than 10 minutes, parameters which are compatible with penetration ability [15].

Doppler duplex penile ultrasonography may have predictive value for sexual function recovery. Ohebshalom [16] demonstrated by using this method the occurrence of up to 71% abnormal penile hemodynamic after prostatic surgery and some cases with venous leak, as well as a strong correlation between erectile function scores domains and abnormal findings during Doppler duplex penile ultrasonography.

Clinical predictive factors for erectile function recovery after radical prostatectomy may be the following [17]:

- Preoperative factors:
  - Young age of the patient and younger partner results in stimulating sexual interest and desire.
  - Good preoperative sexual function: patients with good preoperative sexual function may be the best candidates for nerve-sparing radical prostatectomy with good recovery prognosis. Those who already have sexual dysfunction and use phosphodiesterase type 5 inhibitors may develop worse sexual function irrespective of the surgical technique.
  - Comorbidities: patients with diabetes, arterial hypertension, ischemic heart disease, smokers or with hypercholesterolemia may already have sexual dysfunction.
- Intraoperative factors:
  - Preservation of both neuro-vascular bundles that are neuro-vascular networks more complex than previously anticipated by classic anatomy.
  - Preservation of accessory pudendal artery if present.
  - Surgeon's experience is an independent predictive factor for postoperative preservation of sexual function.

### **ERECTILE FUNCTION AFTER COLONIC AND RECTAL SURGERY**

The prevalence of erectile dysfunction after colonic and rectal surgery varies largely depending of technique used in intention to treat, extension and site of the tumor and associated radiation and chemotherapy. Any surgical technique that produces complete damage of parasympathetic component of pelvic plexus results in complete erectile dysfunction.

Pelvic surgery for benign diseases results in erectile dysfunction in 0-20 % of cases. Abdomino-perineal rectal resection produces erectile dysfunction in 33%-95 % and even in 100 % of cases [Davies 1975, Groliger 1951, quoted by 18]. Recent reports are more optimistic. Abdomino perineal rectal excision produces erectile dysfunction in 40 % of cases and in the best hands proctocolectomy is associated with erectile dysfunction in 2 % of cases [19].

Mezorectal excision with autonomic nerve preservation may preserve erection in 80.9 % of patients and penetration in 75 %. Sexual function and overall satisfaction with relationship are adversely affected by age over 60 years and lower rectal cancer [20]. This operation preserve sexual function in 90 % of patients if it is performed without lateral node dissection and only in 50 % of cases with lateral nerve dissection [21].

Low anterior resection with total mezorectal excision with parasympathetic nerve sparing technique may result in erectile dysfunction in 59.6% of patients. The quality of nerve-sparing technique must be assessed by sacral reflex, pudendal evoked potentials and sympathetic skin responses [22].

Extensive surgery for advanced tumors or local recurrences result in erectile dysfunction in 50 % of cases [Mannoerts 2001 quoted by 14]. Sexual function declines immediately after surgery and then have a slow and incomplete trend to recovery.

Those patients receiving chemotherapy have a 1.8 greater risk to develop sexual dysfunction than those without chemotherapy [14]. External irradiation reduces sexual activity from 71 % before procedure to 56 % after treatment [23].

Laparoscopic approach allows autonomic nerve preservation and even with previous irradiation sexual function is good in 62.5 % of cases, fair in 15.6 % and weak in 21.9 %. Ejaculatory volume may be reduced and retrograde ejaculation may occur in 25 % of patients [24]. Laparoscopic surgery for sigmoid cancer allows preservation of erectile function in 93.2 % of patients and a good ejaculatory function in 93.2 % [25].

### **REHABILITATION OF SEXUAL FUNCTION AFTER RADICAL PROSTATECTOMY, COLONIC AND RECTAL SURGERY.**

The prevention of erectile dysfunction after pelvic surgery involves computed tomography and Doppler ultrasound identification of Denonvilliere's fascia, nerve anatomy and accessory pudendal artery. The prevalence of erectile dysfunction is significantly lower bilateral nerve-sparing surgery or robotic- assisted surgery. Patients may have extensive information about iatrogenic erectile dysfunction after pelvic surgery, their preoperative function must be assessed using validated questionnaires, the immediate postoperative function must be also investigated and rehabilitation programs must be started as soon as possible. A team formed of surgeon, sexologist, patient and his partner is needed. Late attempts for rehabilitation is associated with compromised erectile tissue and function [8].

The key of penile rehabilitation after pelvic surgery is to maintain artificial erections in order to provide a good blood supply and oxygenation of cavernous tissue, if there are not nocturnal erections, and to reduce smooth muscle apoptosis and fibrosis [8].

Experimental and clinical data support the protective role of phosphodiesterase type 5 inhibitors against development iatrogenic erectile dysfunction [2,3,8]. In experimental conditions PDE5 inhibitors administered immediately after cavernous nerve injury for 6 month is followed by cavernous muscle mass increase with 51%-52.6 % compared with non treated animals [17]. PDE5 also improve endothelial function in humans [8,17]. Early treatment with sildenafil citrate increases expression of caveolin-1 and actin which are presumed to preserve cavernous tissue [1].

Padma Nathan [2003, quoted by 6] made the first placebo-controlled study on penile rehabilitation after nerve-sparing prostatectomy. Every evening treatment with sildenafil citrate improves penile rigidity at the base and the tip of the penis in a dose-dependent way and sexual function is significantly better than placebo [26]. PDE5 inhibitors are the first line choice therapy for penile rehabilitation in iatrogenic surgically –induced erectile dysfunction. After 3 years follow-up 31 % of patients treated with sildenafil increased the dose and 37 % stopped the treatment due to recovery of spontaneous erections. The effects of sildenafil proved to be similar in those with bilateral as well as in those with unilateral nerve sparing surgery [27].

They are most effective in young patients with normal preoperative erectile function, after bilateral nerve-sparing radical prostatectomy, but are also effective and may be used in other surgically iatrogenic erectile dysfunction [3].

There was noticed a better compliance for sildenafil rehabilitation treatment in clinical trials than in other individuals due to high cost of therapy [28].

Intracavernous injections or intra urethral delivery (Medicated Urethral System for Erection = MUSE) of erectogenic drugs such as prostaglandin E1 (PGE1-alprostadil) is an option to obtain sustained blood perfusion and oxygenation of corpora cavernosa [11]. Intracavernous PGE1 - 5 mg once or twice weekly beginning one month after surgery, followed by sildenafil citrate after recovery of spontaneous erections results in recovery of sexual function in 56 % of patients with bilateral nerve-sparing prostatectomy and in 37.5 % of those with unilateral nerve preservation. Mean recovery time was 7 month, 42 % of patients regain sexual ability after one year in the first year compared with 8 % in placebo group [29]. PGE1 in association with atorvastatin increases the efficacy of sexual rehabilitation [8].

Vacuum constriction devices (VCD) allow blood flow and oxygen supply independently of cavernous tissue innervation and in absence of spontaneous nocturnal erections [8]. Constrictive ring of VCD maintained blood trapped within the penis for appropriate oxygenation [30]. The use of VCD and PDE5 inhibitors result in positive effects in 14%-81 % of patients following nerve-sparing prostatectomy and in 43%-93% in patients following robotic-assisted laparoscopic surgery [31]. In classic nerve – sparing prostatectomy recovery of sexual function varies from 16 % to 86 % [4].

#### **THE PLACE OF TESTOSTERONE IN IATROGENIC ERECTILE DYSFUNCTION REHABILITATION**

Physicians use not to treat hypogonadal men after radical prostatectomy with testosterone for fear to stimulate prostate cancer cells remained after surgery. There are little evidence for such a simulation [10]. Testosterone stimulates nitric oxide synthase, expression and activity of type 5 phosphodiesterase and reduces the risk for venoocclusive disease. Most data demonstrate that is not reason to stop androgen therapy after successful prostatectomy in hypogonadal men but usual monitoring of PSA and digital rectal examination are mandatory [32].

The rehabilitation program may use the following steps according to the degree of response [Nandipanti 2006]:

- first line therapy PDE 5 inhibitors;
- for non responders to the maximal dosage: intracavernosal or intraurethral erectogenic drugs PGE1 (alprostadil) or VCD;
- the last option are penile prosthesis.

#### **OTHER OPTIONS FOR REHABILITATION IN IATROGENIC ERECTILE DYSFUNCTION**

Oxidative stress-associated tissue damage following bilateral cavernous nerve injury may be reduced by simultaneous administration of immunophilin ligand FK506 in association with sildenafil citrate, which in experimental conditions proved antioxidant enzymes (glutathione peroxidase) and total Akt, an antiapoptotic factor [9]. Immunophilin ligands may represent an alternative for erectile function preservation after cavernous nerve injury [33].

Sartans. Angiotensin type 2 receptor antagonist losartan reduces vasoconstriction induced by angiotensin and smooth muscle fibrosis due to TGF  $\beta$ 1 and may be useful in future rehabilitation programs [34].

Atorvastatin in dose of 10 mg daily for 90 days after surgery significantly improves in association with sildenafil erectile function scores and vaginal penetration [35].

Erythropoetin – a single injection of 40,000 IU in the postoperative day improves patients ability to perform sexually after prostatic surgery [36].

The transfer into corpora cavernosa of Super enzyme, an engenerated protein with prostacyclin synthase activity, which converts arachidonic acid into prostacyclin PGI (2) a vasodilatatory and antiagregant agent would increase blood flow, and prevent apoptosis and fibrosis [37].

Gene therapy and growth factors are still in trials.

## CONCLUSIONS

Radical prostatectomy and colonic and rectal surgery are associated with iatrogenic erectile dysfunction due to cavernous nerve injury which leads to reduced or absent spontaneous erection, hypoxia, oxidative stress, apoptosis of cavernous smooth muscle, fibrosis and venoocclusive disease.

The prevalence of iatrogenic ED depends of type of surgery, autonomic nerve-sparing abilities, and sexual function before surgery.

Postoperative rehabilitation of sexual function program must start immediately after surgery in order to induce erections with adequate blood and oxygen supply to prevent cavernous muscle apoptosis and fibrosis and to increase future ability to perform a good sexual function.

First line therapy in rehabilitation programs are PDE 5 inhibitors, intracavernous erectogenic drugs administration and vacuum constriction devices.

Other options such as antioxidants, sartans, atorvastatin and geen therapy are in trial.

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