FACULTY OF HEALTH AND MEDICAL SCIENCES
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PhD thesis

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Transcutaneous mechanical nerve stimulation in the prevention and treatment of post-prostatectomy erectile dysfunction and urinary incontinence

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Preface and acknowledgements

In 2008, I had the pleasure of attending the American Urological Association's annual congress in Orlando, USA with Professor Jens Sønksen. On this trip we discussed the ideas, which formed the background for this thesis. The first draft for one of the study protocols described here was written on the airplane home.

The thesis itself is based on two clinical trials and includes two original articles exploring the possible role of transcutaneous mechanical nerve stimulation (TMNS) through penile vibratory stimulation following radical prostatectomies. The first paper explores the role in restoration of urinary continence and erectile function in the early post-operative period and the second paper represents an attempt to treat post-prostatectomy incontinence with TMNS. My work was carried out at the Department of Urology at Herlev University Hospital and there I have enjoyed the support and encouragement from colleagues and staff. The first project has been completed with the collaboration of the Department of Urology, Skejby Hospital, Aarhus, Denmark.

First and foremost I would like to thank my advisor and friend Professor Jens Sønksen for our collaboration. It has been a true pleasure and inspiration. I am more than confident that both our professional relationship and personal friendship will last a lifetime. I would also like to thank another good friend, Dr. Dana Ohl from the Department of Urology, University of Michigan. Dr. Ohl has contributed significantly to the design one of my studies and I had the pleasure of spending 2 months working with clinicians and researchers at his department in Ann Arbor, Michigan, USA during my time as a PhD-student.

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Papers included in the thesis

This thesis is based on the following papers:

Mikkel Fode, Michael Borre, Dana A. Ohl, Jonas Lichtbach, Jens Sønksen. **Penile vibratory stimulation in the preservation and restoration of urinary continence and erectile function after radical prostatectomy: A randomized, controlled trial (submitted).**

Mikkel Fode, Jens Sønksen. **Penile vibratory stimulation in the treatment of post-prostatectomy incontinence: A randomized pilot study (submitted).**

English Summary / abstract for publication

A radical prostatectomy (RP) often causes erectile dysfunction (ED) and urinary incontinence (UI). Current means of preventing and treating these side effects are not always effective.
Transcutaneous mechanical nerve stimulation (TMNS) has previously been shown to activate the nerves of the pelvic floor in spinal cord injured men, and it has been used in the treatment of UI in women. The objective of this PhD-thesis was to explore the role of TMNS by penile vibratory stimulation in the prevention and treatment of post-prostatectomy ED and UI. The thesis is based on two randomized studies.

Study 1

The first study included men who were scheduled for nerve sparing RP. The primary end points were International Index of Erectile Function 5 (IIEF-5) score and time to continence after the surgery. An active treatment group was given a TMNS device to use daily at least one week before surgery and subsequently for six weeks after catheter removal. A control group received normal instructions in pelvic floor muscle training. Data from 68 men were available for analyses. There were no statistically significant differences in the groups regarding postoperative ED or UI. However, the IIEF-5 scores were numerically better in the treatment group at each follow up and the difference reached borderline significance with median scores of 18 vs. 7.5 in the control group ($p=0.09$) at 12 months.

Study 2

The second study included men with UI ≥12 months after RP. The primary end point was changes in a 24-hour pad test. In this 12-week-study, one group received daily TMNS for the first 6 weeks, while another group acted as untreated controls. For the next six weeks, the second group received TMNS while the first group was observed. Data from 31 patients were available for analyses. In the early treatment group there were significant reductions in both the 24-hour pad test (median change, -33 g ; $p=0.021$) and in daily UI episodes (median change, -1 episode ; $p=0.023$) at 6 weeks, while no significant changes were seen in the delayed treatment group. Between week 6 and week 12 there was a non-significant decrease on the pad test in the delayed treatment group (median change, -8 g ; $p=0.10$). Pooled analyses of patients from both groups from before and after TMNS showed an overall median change on the 24 hour pad test of -13.5 g ($p=0.004$) after the active TMNS periods.

An overall of 14% of the patients who received TMNS in the two studies had mild, self-limiting side effects including pain and bleeding. No severe side effects were seen in either of the studies.

Conclusion

TMNS is a promising tool in maintaining erectile function following RP and in the treatment of post-prostatectomy UI. However, TMNS was unable to ameliorate all erectile and urinary problems and both the studies were of limited size. Therefore, the findings should serve as background for future research rather than as a basis for clinical recommendations at this time. Future research should focus on exploring alternative treatment protocols with TMNS and on the role of nerve sparing during RP as a predictor for TMNS success.

Danish summary (Dansk resumé)

Radikal prostatektomi (RP) forårsager ofte bivirkninger i form af erektil dysfunktion (ED) og urininkontinens (UI). Nuværende metoder til forebyggelse og behandling af disse problemer er ikke altid effektive. Transkutan mekanisk nervestimulation (TMNS) er tidligere vist at kunne aktivere bækkenbundens nerver hos rygmarvsskadede mænd og metoden er brugt i behandlingen af UI hos kvinder. Formålet med nærværende PhD-afhandling er at undersøge TMNS' potentielle rolle i forebyggelse og behandling af ED og UI efter RP. Afhandlingen er baseret på to randomiserede studier.

Studie 1

Det første studie omhandlede mænd der var indstillet til RP. De primære effektmål var International Index of Erectile Function 5 (IIEF-5) score og tid til kontinens efter operationen. En aktiv behandlingsgruppe fik et TMNS apparat og blev instrueret i at bruge dette dagligt i en periode på mindst en uge før deres operation, og derefter i 6 uger efter kateterfjernelse. En kontrolgruppe modtog udelukkende instruktion i bækkenbundstræning. Data fra 68 deltagere var tilgængelige i analyserne. Der var ikke statistisk signifikant forskel mellem grupperne i forhold til postoperativ ED og UI. Dog var IIEF-5 scorerne numerisk højere i behandlingsgruppen ved hver opfølgning og forskellen grænsede til det signifikante med IIEF-5 medianscorer på 18 i behandlingsgruppen og 7.5 i kontrolgruppen 12 måneder efter operationen (p=0.09).

Studie 2

Det andet studie undersøgte mænd der led af UI mindst 12 måneder efter RP. Det primære effektmål var ændringer i en 24-timers blevejningstest. I dette 12 ugers studie, modtog én gruppe daglig TMNS behandling i de første 6 uger, mens en anden gruppe fungerede som kontroller. I de næste 6 uger modtog den anden gruppe TMNS behandling, mens den første gruppe blev observeret. Data fra 31 deltagere var tilgængelige i analyserne. I den gruppe der modtog tidlig behandling, var der statistisk signifikante reduktioner i både 24-timers blevejningstest (median ændring, -33 g ; p=0.021) og i antallet af daglige inkontinensepisoder (median ændring, -1 episode ; p=0.023) efter 6 uger, mens der ikke var nogen signifikante ændringer hos observationsgruppen. Mellem 6 og 12 uger var der et ikke-signifikant fald i vægten af 24-timers blevejningstesten i gruppen der modtog sen TMNS-behandling (median ændring, -8 g ; p=0.10). En samlet analyse af patienterne i begge

grupper før og efter TMNS viste en median ændring i 24-timers blevejningstesten på -13.5 g (p=0.004) efter perioderne med aktiv TMNS.

Samlet set oplevede 14 % af de deltagere der modtag TMNS i de 2 studier milde, ikke-behandlingskrævende bivirkninger inklusiv smerte og blødning. Der var ingen alvorlige bivirkninger i studierne.

Konklusion

TMNS er et lovende værktøj i forebyggelse af ED og i behandlingen af inkontinens efter RP. Dog er det vigtigt at understrege, at TMNS ikke var i stand til at løse alle problemerne omkring de to tilstande og at studierne begge havde relativt få deltagere. Derfor bør vores fund bruges til at danne baggrund for yderligere forskning frem for kliniske anbefalinger på nuværende tidspunkt. Fremtidig forskning bør fokuseres på at afprøve alternative TMNS-behandlingsprotokoller og på at undersøge den rolle nervebevarelse under RP spiller for succes med TMNS-behandling.

Abbreviations

DAN-PSS: Danish Prostate symptom score

ED: erectile dysfunction

ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form

IIEF-5: International Index of Erectile Function-5

IPSS: International Prostate Symptom Score

LUTS: Lower urinary tract symptoms

NO: Nitric oxide

PDE5-I: Phosphodiesterase-5 inhibitors

PFMT: Pelvic floor muscle training

PSA: Prostate-specific antigen

RP: Radical prostatectomy

TMNS: Transcutaneous mechanical nerve stimulation

UI: Urinary incontinence

VED: Vacuum erectile device

Objective and hypotheses

The objective of this PhD-thesis is to explore the possible role of transcutaneous mechanical nerve stimulation (TMNS) by penile vibratory stimulation in the prevention and treatment of erectile dysfunction (ED) and urinary incontinence (UI) after radical prostatectomy (RP). This is done based on three hypotheses:

1. TMNS in the early post-operative period after nerve-sparing RP can stimulate the cavernous nerves and aid in the restitution from neuropraxia, thereby improving long term erectile function.

2. TMNS in the early post-operative period after nerve-sparing RP can improve urinary control and reduce the time to postoperative continence.

3. TMNS can be used to treat long term UI (minimum one year after surgery) after RP.

Background

Prostate cancer and radical prostatectomies

An increasing number of prostate cancers are being diagnosed and the disease is estimated to account for almost 900,000 yearly cancers worldwide (1;2). If the disease is detected early then curative treatment can be offered (3). Here RP has been shown to decrease mortality from the disease (4). Unfortunately, the procedures carry risks of adverse effects in the form of post surgical ED and UI. In high quality studies, the proportion of patients who suffer from ED after RP has been reported to be anywhere between 20% and 75% (5). The discrepancies can be attributed to differences in patient populations, erectile function before surgery, surgical techniques, data collection, treatments for erectile dysfunction, and especially varying definitions of ED. A case series from Herlev Hospital has found that the rate of ED one year after surgery in patients who were potent preoperatively (n=418) was approximately 70% (Fode et al., paper under peer review). Good preoperative erectile function, younger age at surgery and nerve sparing constituted protectors of potency in this study.

As with erectile dysfunction, UI rates after RP are highly dependent on how successful outcomes are defined (6). One of the most important factors is time after RP, as continence tends to improve gradually at least during the first year after surgery. A 2010 review found UI rates of 17%-77% at 1 month after RP, while they dropped to 7%-53% at 3 months and 3%-38% at 6 months (7). In most studies the rate of UI 12 months after surgery is about 15% (7). The aforementioned case series from Herlev Hospital has demonstrated that approximately 80% of patients were continent at one year follow up (n=772) (Fode et al., paper under peer review). Surgical technique (robot-assisted laparoscopic surgery vs. open surgery), preoperative lower urinary tract symptoms (LUTS), older age and non-nerve sparing RP were all risk factors for long term UI in our series.

Regardless of the exact incidence, it is clear that the side effects after RP are common and that they can have negative effects on patients' quality of life following surgery (8). Therefore, much attention has been devoted to ameliorate the issues. However, in spite of these efforts no completely satisfactory solutions have been found.

Methods of preserving long term erectile function

Generally, there is no doubt, that sparing of the cavernous nerves during surgery is of utmost importance in preserving erectile function following RP and nerve sparing techniques are commonly used when tumor characteristics allow it (9). This is because the induction of normal erections is dependent on nitric oxide (NO) produced by parasympathetic nerve fibers in these nerves (10;11). Thus the recovery of spontaneous erectile function, after non-nerve sparing surgery is rare (12). This means that all attempts at improving spontaneous erectile function after RP (i.a. function either without medications or with oral medications only) are aimed almost exclusively at nerve spared patients in the current literature. However, even with nerve sparing, post-operative ED can occur (5). As an explanation for this, current literature shows that the cavernous nerves are likely disturbed even during true nerve sparing procedures by means of direct trauma, stretching, heating, ischemic effects on nerve tissue, and local inflammatory effects (13;14). This is believed to cause post-operative neuropraxia and a subsequent improvement of function in the anatomically intact nerves can explain why erections may gradually improve up to four years after surgery (15;16).

During the period of neuropraxia, there will be a lack of erections. As oxygen tension in the flaccid penis is only 25-43 mm Hg while it rises to approximately 100 mm Hg in the erect penis, it has been theorized that the period with neuropraxia and missing erections leads to ischemia in the penile tissue (17). This can in turn cause apoptosis of smooth muscle and accumulation of collagen (18;19). As fibrotic tissue cannot expand during erections to compress the venules leading blood away from the penis, these structural changes may then cause permanent veno-occlusive ED (20). This means that the ED will become permanent even if the nerve function returns. The theoretical considerations are supported by several animal studies, which have demonstrated structural alterations in the penile tissue following induced nerve damage (18;21-23). Fibrosis in the cavernosal bodies has also been found in humans following RP (24) and it has been shown that the risk of veno-occlusive dysfunction increases with time after surgery (20).

To prevent long term ED after RP, so-called “penile rehabilitation” programs have been invented to increase cavernosal oxygenation in the early post operative period, and these have gained widespread popularity (25-27). The most commonly used method is treatment with oral phosphodiesterase-5 inhibitors (PDE5-I), which has shown promise in animal studies (28-36). The first evidence that PDE5-I could have an effect in humans came from a pilot study exploring the

effects of sildenafil after nerve sparing RP (37). Forty patients were randomized to either sildenafil 50 mg or sildenafil 100 mg every other night for 6 months following surgery. Biopsies were taken immediately before surgery and after 6 months. Patients in the 50 mg dose group showed no statistically significant decrease in the mean content of smooth muscle (51.5% vs. 52.7% ; p=0.81). Meanwhile, patients in the 100 mg group showed an increase from a mean preoperative smooth muscle content of 42.8% of biopsy tissue to a mean postoperative content of 56.9% ($p < 0.05$). A similar study was performed by Iacono and co-workers (38). Here 21 patients received sildenafil 50 mg, 3 times a week, for two months following RP. Cavernosal biopsies were taken before surgery and after the two months of treatment, and they showed that neither the content of connective tissue or elastic fibers had changed significantly over the course of the study. Unfortunately neither of the studies had a placebo arm, and it is possible that the results simply represent successful nerve sparing procedures. In addition it is unclear if the preservation of smooth muscle tissue improved erectile function.

Two randomized and placebo controlled studies have investigated the clinical effects of PDE5-I after RP with erectile function as the main outcome parameter. Both studies recruited men who underwent bilateral nerve-sparing RP. In the first study, the patients were randomized to receive nightly doses of 100 mg sildenafil, 50 mg sildenafil or placebo respectively (n=76) (39). After 9 months of treatment and a subsequent wash-out period, 14/51 patients who completed active PDE5-I treatment had satisfactory erectile function (27%). There was no significant difference between patients who had received 50 mg of sildenafil or 100 mg sildenafil. In the placebo group only 1/25 patients reached satisfactory erectile function (4%). In the second study (n=423), the participants received either 10 mg vardenafil nightly, on-demand vardenafil, or placebo for 9 months following surgery (40). Following wash-out, there were no statistically significant differences in erectile function between the three groups. The investigators then offered the participants a 2 month open label treatment with on-demand vardenafil to assess if the penile rehabilitation program had increased the long term effects of the drug. However, during the open label phase, there were still no significant differences in erectile function between the groups. A third randomized – but not placebo controlled – study has investigated the effects of the longer acting PDE5-I, tadalafil, after bilateral nerve sparing RP (41). Here, 65 men were randomized to either recieve 20 mg of tadalafil three times a week for 6 months or to a no treatment group.

Erectile function was assessed at 12 month after surgery, and here the authors found no significant differences between the two groups.

Vacuum erection devices (VED) have also been attempted in penile rehabilitation. These have shown promise in animal studies (42;43). However, the results in humans have been disappointing as the 2 randomized trials performed to date have shown no benefit on long term erectile function. In the first study, Kohler and co-authors randomised 28 men to two different protocols of VED treatment after nerve sparing RP (44). One group started treatment 1 month after their surgery and was instructed to apply the VED for two 5 minute periods daily without a constriction band and for intercourse as desired. The other group received no treatment in the first period after their surgery while they were given a VED to use for intercourse after 6 months. At 6 months both groups were also offered PDE5-I. At 12 month follow-up, there was no difference in erectile function between the groups ($p=0.75$) and no spontaneous erections adequate for intercourse were reported in either group.

In the second study, Raina et al., randomized 109 patients to daily VED for 9 months following RP or to no treatment (45). At 9 month, 10/ 60 patients (17%) in the VED group reported return of natural erections sufficient for intercourse, while this number was 4/35 patients (11%) in the no treatment group. The study failed to report a p-value for this finding, and it was concluded that VED had been effective. However, when analysing the data from the paper using a chi squared test, the difference is not statistically significant ($p > 0.05$). Therefore the study cannot be taken as support of the use of VED in penile rehabilitation.

The final treatments, which are commonly used in penile rehabilitation, are injection therapy and urethral suppository treatment with Prostaglandin E1. In fact, the very first attempt at penile rehabilitation was performed by Montorsi et al. in 1997 with injections of prostaglandin E1 (46). Here, 30 patients were randomized to treatment or control after nerve sparing RP. The treatment group received intracavernosal injections of alprostadil three times/week for 12 weeks. In the treatment group, 12 patients completed the study. According to the study protocol, patients were considered to have regained spontaneous erectile function if they needed prostaglandin injections with less than 50% of attempts at intercourse. This goal was achieved by eight patients in the treatment group (67%) and by three patients in the control group (20%). In addition, 10 (67%)

patients in the control group reported to achieve erections insufficient for intercourse in most cases. While these results are promising, it is important to note the limitations of the study, which include a lack of preoperative assessment of erectile function and the reliance of subjective patient histories as the main outcome (no validated questionnaires were used). No subsequent randomized studies have tested scheduled penile injection therapy after RP as a means of improving spontaneous erections.

To date, no randomized studies have compared urethral suppository treatment with placebo.

Methods of preventing and treating post-prostatectomy incontinence

The most common cause of UI following RP is believed to be weakness of the urethral sphincter (47;48). This can be caused by direct damage or scaring of the sphincter, but it is likely that nerve damage plays an important role in many patients. Thus, the musculature of the sphincter is innervated by the pudendal nerve, which can be damaged during surgery (49;50). Meanwhile, the pudendal nerve also constitute the main nervous supply to the pelvic musculature including the levator ani muscle, which is an important part in normal urinary continence through closure of the urethra (51). In addition, anatomical studies have shown that fibers branching off from the cavernous nerves may also contribute to the innervation of both the urinary sphincter and the levator ani musculature (52;53). Finally, bladder dysfunction, in the form of detrusor instability or impaired bladder compliance may also play a role in post-prostatectomy UI, perhaps due to bladder denervation during surgery (47;48;54). Accordingly, it has been shown that preservation of pudendal nerve fibers may lead to a more rapid return of urinary continence following RP (55;56). Sparing of the cavernous nerves has also been associated with better continence outcomes after RP compared to non-nerve sparing surgery, although discrepancies do exist in the literature (57).

The mainstay of conservative treatment and prevention of UI is pelvic floor muscle training (PFMT) with or without biofeedback (58). However, no consensuses exist on how instruction should be given or on the exact timing of the intervention and findings in the literature are contradictory regarding efficacy. The evidence from randomised or quasi-randomised controlled trials was summarized in a Cochrane review published in 2012 (59). The authors were unable to find an overall effect of PFMT versus no treatment, sham therapy or verbal instruction when offered

as a treatment to men with manifest UI after surgery. In contrast, trials that used PFMT for prevention showed an overall benefit on self reported outcomes with a relative risk for UI of 0.32 (95% CI 0.20 to 0.51) after one year on meta analysis. However, the positive results could not be confirmed by measurements on pad tests. Interestingly, the positive subjective effects were mainly derived from 2 trials, which delivered the instruction after surgery and did not include biofeedback (60;61). Ultimately the authors conclude that more well-designed trials are needed due to considerable variation in the interventions, populations and outcome measures in the literature.

In this context, only few recent trials have been published. A small study (n=32) by Tienforti and co-workers found that PFMT was effective in the prevention of postoperative incontinence on both subjective and objective parameters (62) with 10/16 patients being continent (defined as a score of 0 on the International Consultation on Incontinence Questionnaire) at 6 months compared to 1/16 in the control group (P=0.002). In this study, supervised training sessions were given before surgery and at catheter removal with monthly follow up visits as long as UI persisted. In a larger trial, 332 men who were incontinent at 1 month after RP and who had previously received oral and written information on PFMT were randomized to a PFMT program or a control group (63). Patients in the active treatment group were instructed one-on-one in PFMT with biofeedback on two occasions. They were also submitted to 10 sets of pelvic floor electrical stimulation lasting 15 minutes each. All patients regained self reported continence at one year, but the time to continence was shorter in the treatment group compared to the control group (44±2 days, vs. 76±4 days, $p<0.01$). It is not clear to which extend the benefit was derived from PFMT or from the electrical stimulation. Regarding the timing of treatment, a recent randomized study by Geraerts et al. (n=180) showed, that it does not make a difference in terms of time to post-surgical continence whether instruction in PFMT is started 3 weeks prior to RP or at catheter removal after the surgery (64). However, a similar study by Centemero (n=118) (included in the Cochrane review as an abstract) showed a substantial benefit from starting PFMT 30 days before surgery, as compared to starting the exercises after surgery. Here the risk of UI was reduced by 41% ($p = 0.001$) and 38% ($p < 0.001$) at 1 month and 3 months after surgery respectively (65). The main difference between the studies was that the Geraerts study used a pad test as the main outcome measure while the Centemero study used subjective patient assessment. In both studies the health related quality of life during follow-up was improved in the early exercise groups compared to the late exercise groups.

The Cochrane review also examined the evidence for other conservative treatments, namely electrical stimulation protocols. Three trials investigated electrical stimulation with anal electrodes in the treatment of manifest post-prostatectomy UI (66-68). On meta-analysis these trials showed a reduction in short term (less than 3 months) self reported UI with electrical stimulation compared to control (RR 0.84, 95% CI 0.74 to 0.94). However, the results were not backed up by objective measurements on pad tests and there was no effect on longer term UI. In addition one study (n=60) compared PFMT plus anal electrical stimulation initiated 7 days after catheter removal to verbal/written PFMT instructions (69). This study found a benefit of the intervention in terms of both subjective and objective UI beginning from 4 weeks after the intervention with durability until the end of the study at 6 months. At this time, 97% were continent in the treatment group vs. 67% in the group who received verbal/written PMFT instructions ($p < 0.05$). Another study (n=139), in which treatment was initiated immediately after catheter removal, found no difference between PFMT alone and PFMT plus 15 minutes of anal electrical stimulation with a probe twice daily for 3 months (70). As for PFMT, the final conclusion in the Cochrane review was that more well-designed trials are needed. Unfortunately, only one subsequent study has investigated electrical stimulation. Here, Laurienzo and co-workers compared 15 minutes of preoperative rectal electrical stimulation to both PFMT and to passive control in a group of 49 patients (71). There were no differences in pad tests or health related quality of life between the three groups at 1, 3 and 6 months of follow up.

In addition to electrical stimulation, it is worth mentioning extracorporeal magnetic innervation, which is the use of a magnetic chair to stimulate contraction of the pelvic floor muscles. This method has been attempted immediately after surgery in a small randomized study (72). Here, 36 patients were assigned to 20 minutes of magnetic innervation twice a week for 2 months, 15 minutes of electrical stimulation with an anal electrode twice daily for 1 month, or PFMT. Both magnetic innervation and electrical stimulation showed better outcomes on the 24-hour pad test at 1 and 2 months postoperatively compared to PFMT, while the three groups were similar at 6 months. Likewise, a non-randomized study by Terzoni and co-workers has found that there may be a benefit of magnetic innervation applied after RP as compared to PFMT (73). Thus the study found a 64% continence rate with magnetic innervation compared to a rate of 33% with PFMT at 6 weeks following surgery ($p<0.0001$). Apparently, the difference did not remain significant in the long term, but the reporting from the study is unclear regarding this outcome.

Transcutaneous mechanical nerve stimulation and the neuro-anatomical background

TMNS preformed through vibratory stimulation of the dorsal penile nerve is routinely used to induce ejaculation in men with spinal cord injuries as these patients are generally not able to obtain ejaculation with normal sexual stimulation (74). In their 1994 landmark study, Sønksen et al., discovered that the vibration amplitude is crucial in inducing reflex ejaculation with penile TMNS, as an amplitude of 2.5 mm and a frequency of 100 Hz induced ejaculation in almost 90% of the spinal cord injured men in the study (75). The majority of men had antegrade ejaculations indicating coordinated bladder neck closure. Based on this knowledge, it is clear that penile TMNS can establish a connection to the spinal cord at the centers responsible for ejaculation, namely the parasympathetic nerves at S2-S4 and the sympathetic nerves at T10-T12.

Incidentally, the nerve fibers from the same centers are responsible for erections and for normal urinary control. Thus, parasympathetic fibers from S2-S4 in the spinal cord constitute the efferent limb of the erectile response via the cavernous nerve (9). In addition, parasympathic fibers from S2-S4 and sympathetic fibers from T10-L2 innervate the bladder wall (76), while the urethral sphincter and the pelvic floor muscles are innervated by the pudendal nerve, which also arise from the S2 –S4 roots (49;50). The neuro-anatomical connection between penile TMNS and the aforementioned nerve fibers is that afferent nerve fibers, which are activated with stimulation of the glans penis, course through the dorsal penile nerve and join fibers from the the pudendal nerve (49;50). Through the pudendal nerve the fibers then reach the spinal cord at the levels S2-S4 (49;50). Afferent nerve fibers from the penis also reach the sympathetic center in the thoracolumbar part of the spinal cord and through this connection they may play a role in the control of the bladder neck and the detrusor muscle (77). The latter point is illustrated in a number of studies, which has shown that electric stimulation of the dorsal genital nerve can result in inhibition of detrusor contractions in patients with overactive bladder syndrome (78).

Likely working through the neural pathways described above, a series of studies have shown that genital and perineal TMNS may have beneficial effects with regard to urinary function. In a study with spinal cord injured men, urethral pressure profiles during and after TMNS induced ejaculations, showed significant increases in external sphincter pressure (79). Furthermore 1 month

of TMNS every third day, resulted in increases in bladder capacity in spinal cord injured men suffering from detrusor overactivity (80).

These observations led to the thought that genital TMNS could be used in the treatment of UI in patients who do not suffer from spinal cord injuries. Subsequently, a pilot study demonstrated that TMNS performed on the perineum in healthy women could induce powerful pressure increments of the external urethral sphincter (70-110 cm H_2O), when a vibration amplitude of 2 mm was applied (81). More importantly, weekly perineal TMNS for 6 weeks in 33 women suffering from stress UI, resulted in a significant reduction in daily UI episodes and pad use (82). Complete resolution of symptoms was seen in 24/33 women (74%) and after 3 months of subsequent observation, 22/33 (67%) still reported to be completely dry.

In addition to these findings, clinical experience gathered over the last few years from treating post-prostatectomy UI with TMNS at the Department of Urology, Herlev Hospital has been promising with several patients experiencing relief of symptoms and some experiencing resolution (unpublished data). No significant side effects have been noted in non-spinal cord injured patients to date.

Motivation for the PhD study

As described, ED and UI are common after RP in part due to nerve damage. As RP has been shown to reduce mortality from prostate cancer it will likely continue to be a commonly performed procedure (4). Unfortunately, the effects of current means of ED and UI prevention after RP are questionable and they leave a significant number of patients with long term problems that may require surgical intervention (83;84).

The current methods of penile rehabilitation are all aimed at inducing erections to increase cavernous oxygenation as a way of improving long term erectile function. However, it is generally accepted that the main pathofysiological mechanism behind ED after a nerve sparing RP is likely to be neuropraxia. Therefore it seems logical to aim penile rehabilitation programs at improving post operative nerve function. This may promote a better long term nerve recovery. It may also shorten the period of neuropraxia and thereby reduce the risk of structural changes occurring in the penis. Working through the pathways described above, TMNS may represent a way of stimulating the cavernous nerves following surgery, which may aid in their recovery.

Likewise, disturbance of the pudendal nerve may be a cause of post-prostatectomy UI. There is a body of literature, which shows that TMNS may affect the nerves of the pelvic floor and a pilot study in women has specifically shown an effect on UI (79-81). This means that, pudendal nerve stimulation through TMNS may help speed up the recovery of continence after RP. In addition, TMNS may be of benefit in the treatment of manifest long term urinary UI.

Aim

Study I

The purpose of the first study in the thesis was to examine the effect of short term TMNS in the immediate post operative period after RP in the preservation and restoration of erectile function and urinary continence.

Study II

The purpose of the second study was to examine the effect of TMNS in the treatment of manifest male UI, which was present at least 1 year after RP.

Technical specifications and TMNS protocol in the studies

For both studies, the FERTI CARE® vibrator (Multicept A/S, Frederiksberg, Denmark) was used. TMNS was delivered through a small plastic plate (figure 1). The main advantage of this vibrator is that both vibratory amplitude and frequency can be set precisely. The stimulation parameters in the studies were chosen based on previous research regarding UI in women (82) and on clinical data from treating post-prostatectomy UI with penile TMNS at Herlev Hospital (unpublished data). The device was set to a vibration frequency of 100 Hz and an amplitude of 2 mm. In both studies, the participants were instructed in stimulating the ventral surface of the glans corresponding to the area of the frenulum. The foreskin was retracted during the stimulation. After the participants had received oral and written instruction along with an in clinic demonstration of the device, they were instructed in performing daily stimulation sequences in their own home consisting of 10 seconds of stimulation followed by a 10 second pause repeated 10 times (for a total of 100 seconds of stimulation every day). Participants were asked to take note of any side effects experienced with the treatment and to take a break from the stimulations if the skin of the penis became red, swollen or painful.

Due to the nature of the intervention, both trials were non-blinded. The study group has previously attempted to construct a sham TMNS device by eliminating the vibration amplitude through tampering with the motor of the FERTI CARE® vibrator. We successfully eliminated the amplitude, however, the alteration was obvious to both healthcare providers and patients making the blinding procedure unsuccessful.

Materials and methods

Study I

The first study was a randomized controlled trial conducted at the Departments of Urology at Herlev Hospital and Skejby Hospital between July 2010 and March 2013. Originally the study was designed to only include patients who were scheduled for open retropubic RP at Herlev Hospital. However, the surgical technique was gradually changed to be mainly robotic early in the study period, which meant that we decided to change the study protocol to also include patients who underwent robot-assisted RP. In addition, difficulty to recruit a sufficient number of patients meant that Skejby Hospital was included as a study site in the fall of 2011.

Men who were scheduled to undergo unilateral or bilateral nerve sparing RP were eligible for the study. Participants had to be fully continent before surgery (as assessed by the validated Danish Prostate symptom score (DAN-PSS) (85)), and sexually active with an International Index of Erectile Function-5 (IIEF-5) (86) score of at least 18 without erectogenic aids. As patients were allowed oral PDE5-I after surgery, our exclusion criteria included any condition which would prevent the participant from receiving such medications.

Data regarding tumor characteristics, preoperative erectile function (assessed by the IIEF-5 questionnaire), and preoperative LUTS (assessed by the DAN-PSS questionnaire) were collected at inclusion. Participants were randomized by a draw using opaque envelopes to either a TMNS group or a control group. In both groups the patients received one preoperative session with PFMT instruction, in accordance with the normal standard at Herlev Hospital. Patients in the TMNS group also received instruction in using the FERTI CARE® vibrator. These patients were then given a FERTI CARE® vibrator and asked to use the device daily in their homes for at least 1 week prior to RP. In conjunction with surgery, the laterality of nerve sparing (bilateral/unilateral/non nerve sparing) was noted in all patients and those who underwent non-nerve-sparing procedures were excluded from the study. Following RP, patients in the TMNS group were instructed to resume daily stimulation at catheter removal and to continue the daily sessions for 6 weeks. Participants in both groups were contacted by phone at 2 and 6 weeks following RP to ensure compliance with PFMT and TMNS. Patients in the TMNS group were asked systematically about side effects at each phone call and asked to contact the scientific staff if side effects arose between contacts. All participants were offered on-demand or daily PDE5-I treatment approximately 1 month after

surgery and at subsequent follow-up visits after this. It was left up to the patients if they wished to receive this treatment at all time points during follow-up.

Participants were evaluated at 3, 6 and 12 months following RP. The IIEF-5 questionnaire was used to assess erectile function and patients were asked to rate their continence on a scale from 1 to 4 (1 = Completely dry, 2 = Use of maximum one pad per day for security reasons only, 3= Mild incontinence, 4 = Severe incontinence) and to report their use of pads/diapers on a specific questionnaire used at the Department of Urology, Herlev Hospital. In addition the DAN-PSS questionnaire was used to assess urinary bother at each follow up. Patients reporting to use up to one pad daily for security reasons only were considered continent for purposes of the study.

The primary end point regarding erectile function was the difference in median IIEF-5 scores 12 months after RP between the groups. The primary endpoint regarding continence was time to continence following surgery. Secondary outcome measures regarding erectile function included IIEF-5 scores at 3 and 6 months after RP and the number of patients who achieved an IIEF-5 score of at least 18 with or without PDE5-I during the follow-up period. Secondary outcome measures regarding urinary function included the overall difference in reported pad use and the difference in median postoperative DAN-PSS.

All patients provided written, informed consent and the study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Danish ethical counsel and the Danish Data Protection Agency. It was registered at www.clinicaltrials.org (NCT01067261).

Study II

The second study was conducted between July 2012 and June 2013 as a 12-week randomized trial at the Department of Urology, Herlev University Hospital. Patients were eligible for the study if they were bothered by UI and had a pad test showing a loss of at least 8 g of urine per 24 hours at a minimum of 1 year after RP. Exclusion criteria were UI prior to surgery, adjuvant radiation or hormonal therapy following RP, surgical treatment for UI and acute or chronic illness, which could affect urinary function. For the latter criteria, a urinary dipstick analysis and subsequent urine culture if relevant were performed to rule out urinary infections and to raise suspicion of untreated diabetes at all study visits.

Data regarding tumor characteristics, nerve sparing at surgery and baseline UI were collected at inclusion. Data regarding UI included a 24-hour pad test and a 72 hour voiding diary as recommended in the European Association of Urology guidelines (58). In addition, the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) (87), the International Prostate Symptom Score (IPSS) (88), and a global assessment question were used for subjective assessment (possible answers were: "Very satisfied", "Partly satisfied", "Neither satisfied nor dissatisfied", "Partly dissatisfied" and "Very dissatisfied").

Participants were randomized to two groups based on a computer generated list and the allocation sequence was implemented through numbered opaque envelopes. Group 1 (the immediate treatment group) was received TMNS treatment for the first 6 weeks of the study while group 2 (the delayed treatment group) served as controls. During the final 6 weeks of the study the groups were set to switch so that group 2 would receive TMNS treatment during this time. No lifestyle advice regarding urinary function was given and participants were instructed to refrain from changing habits for the 12 week duration of the study. All patients were instructed in use of the FERTI CARE® vibrator as described above. The patients were given a device to use daily in their homes for their respective 6 week treatment periods. All participants were followed up at 6 and 12 weeks with a 24-hour pad test, a 72 hour voiding diary, the ICIQ-SF and the IPSS questionnaire corresponding to the baseline measurements. After TMNS treatment they were also given a global assessment question as described above and they were asked if they would recommend the treatment to others.

The primary outcome measure was the change in leakage between baseline and 6 weeks on the 24-hour pad test in the two groups. Secondary outcome measures were changes in the 24-hour pad test at 12 weeks, the change in the number of UI episodes at 6 and 12 weeks, changes in IPSS and ICIQ-SF symptom scores as well as global satisfaction and attitudes toward TMNS recommendations. In addition, pooled analyses of outcomes in both of the two groups before and after TMNS were performed.

All patients provided written, informed consent and the study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Danish ethical counsel and the Danish Data Protection Agency. It was registered at www.clinicaltrials.org (NCT01540656).

Statistics

The sample size in study 1 was calculated based on the IIEF-5 questionnaire. With a two sided significance level set at 0.05 it was calculated that 64 patients would be needed to detect a minimally clinically meaningful difference of 5 with a standard deviation of 6 and a power of 80%. To account for subsequent exclusion, drop out and anticipated non compliance we aimed at including 80 patients in the pre-operative phase.

As there is no predefined minimally clinically meaningful difference on pad tests and as we did not know the range and standard deviation of the pad tests in our participants before initiating the study, we were unable to conduct a formal power analysis in the second study.

Non-parametric statistics were performed for all outcome measures with the SAS version 9.2 statistical software package for windows (Institute Inc., Cary, NC, USA). For non-paired analyses, the Wilcoxon-Mann-Whitney test was used to assess differences in continuous parameters while Fisher's exact test or the chi squared test was used with regard to categorical variables. The Wilcoxon signed rank test was used for paired analyses. All values are reported as either percentages or as medians and range.

Results

Prevention of post-prostatectomy erectile dysfunction

A total of 83 patients were included preoperatively and 15 patients were subsequently excluded from the study. The flow of patients is illustrated in figure 2. There were no significant differences regarding robot/open surgery (p=0.66), Gleason score (p=0.59), tumor stage (p=0.81), age (p=0.58), pre-operative IIEF-5 score (p=0.49), pre-operative DAN-PSS (p=0.32) or tumor volume= (p=0.94) between the final 68 patients and the 15 excluded patients. Naturally, there was a higher degree of nerve sparing in the included patients (p<0.0001) as five patients had been excluded on the basis of a non-nerve-sparing surgery. In addition, the excluded patients had higher prostate-specific antigen (PSA) values with a median of 9.3 (range 4.9-48) vs. 7.4 (range 0.6-20) in the included patients (p=0.044).

All together data from 68 patients were available for analysis (30 patients randomized to vibration therapy and 38 patients randomized to the control group). There were no significant differences in patient or tumor characteristics between groups, except that patients randomized to the TMNS group had significantly more LUTS prior to surgery (p= 0.048) (tables 1 and 2). Follow-up data was available for 64/68 patients at 3 months, 67/68 patients at 6 months and 68/68 patients at 12 months.

The IIEF-5 score was higher in the TMNS group at all time points after surgery but the difference between groups only reached borderline statistical significance with a median IIEF-5 score of 18 (0-25) in the TMNS group at12 months vs. a score of 7.5 (0-25) in the control group (p=0.09) (table 3). Standard deviations for the 12 months IIEF-5 scores were 8.3 and 8.6 in the treatment and the control groups respectively. At 12 months post surgery 16/30 (53%) patients in the TMNS group had reached an IIEF-5 score of at least 18 while this was the case for 12/38 (32%) patients in the control group (P=0.07). There was also a non-significant trend toward higher IIEF-5 scores and more men returning to an IIEF score of at least 18 at 6 months (table 3).

Prevention of post-prostatectomy urinary incontinence

Patient characteristics are described above under "**Prevention of post-prostatectomy erectile dysfunction"** and listed in tables 1 and 2**.** Of note, patients randomized to the TMNS group had significantly more LUTS according to the DAN-PSS questionnaire prior to surgery (p= 0.048).

There were no significant differences in the proportions of continent patients between groups at either 3, 6 or 12 months after surgery (table 4). At 12 months 90% of the TMNS patients were continent while 94.7% of the control patients were continent (P=0.46). There was a non-significant trend toward a higher number of pads in the TMNS group at 3 months (0.09) while there were no differences at 6 and 12 months (table 4). Likewise, there were no significant differences in DAN-PSS scores between groups at any point after the surgery (table 5).

Due to the skewed DAN-PSS with randomization between the groups, post hoc analyses were conducted to assess if the preoperative DAN-PSS was associated to urinary outcomes. These analyses showed that a high preoperative score was associated with UI at 12 months (p= 0.035) and with postoperative DAN-PSS at all time points during follow up (data not shown).

Treatment of post-prostatectomy urinary incontinence

A total of 69 possible participants were identified based on hospital records and contacted. In addition one patient was referred for the study from a neighbouring centre. Thirty-nine patients were randomized and 8 of these patients were subsequently excluded.The flow of patients is illustrated in figure 3. There were no statistically significant differences between the 8 excluded patients and the 31 included patients regarding age (p= 0.8), robotic vs. open surgery (p=0.39), tumor characteristics, baseline 24-hour pad test (p=0.26), daily UI episodes at baseline (p=0.95), baseline IPSS (p=0.48) or baseline ICIQ-SF scores (p=0.21). However only 1/8 of the excluded patients had undergone nerve sparing surgery compared to 17/31 of the included patients (p= 0.05).

In total, 31 patients completed the first 6 weeks of the study (15 belonged to group 1 and 16 belonged to group 2) and 30 patients completed the entire 12 weeks (15 in each group). There were no significant differences in patient or tumor characteristics between groups (tables 6 and 7). No patients had signs of biochemical recurrence at the time of inclusion and no patients had received adjuvant radiation or androgen deprivation therapy.

All study participants completed diaper tests, questionnaires and voiding diaries according to the study methods. According to the ICIQ-SF, all patients lost urine on physical strain indication stress UI. Twenty-three patients (12 in group 1 and 11 in group 2) reported the number of UI episodes on

their voiding diary. The remaining 8 patients all reported to leak urine frequently but without noticing each incident.

There was a significant reduction in the 24-hour pad test in group 1 at 6 weeks compared to baseline, with a median change of -33 g (-335 g to +48 g ; p=0.021). In group 2 there was a non-significant reduction at 6 weeks with a median change of -4 g (-183 g to +89 g ; p=0.36). At 12 weeks the improvement in group 1 remained significant compared to baseline (median change of -28 g ; range -163 g to +31 g ; p=0.04). In the delayed TMNS group there was a borderline significant median decrease on the pad test between 6 weeks and 12 weeks with a change of -8 g (-49 g to +33 g ; p=0.10). Overall, 12/15 (80%) patients had reductions on the diaper test in group 1 between baseline and 6 weeks and for 8 of these patients the improvement was maintained at 12 weeks. In group 2, 11/15 (73%) patients had reductions in urinary loss between 6 and 12 weeks.

There was a significant median reduction in the number of UI episodes in group 1 at 6 weeks compared to baseline with a change of -1 (-3.5 to +1) daily episodes (p=0.023). In group 2 there was a non-significant median increase of 0.4 (-3.7 to +3) daily episodes (p=0.54) per day at 6 weeks. At 12 weeks the decrease in UI episodes remained significant compared to baseline in group 1 with a median change of -1 (-3.3 to +0.4) daily episodes (p=0.008). There was no significant change in the number of UI episodes between 6 and 12 weeks in group 2 with a median change of -0.3 (-2 to +4) daily episodes (p= 0.71).

Pooled analyses of both groups showed a significant overall median decrease in urine loss on the 24 hour pad test with a change of -13.5 g (-335 g to +48 g ; p=0.004) and a borderline significant decrease in median daily UI episodes with a change of -0.7 (-3.5 to +49 episodes (p=0.07) between visits before and after TMNS.

To explore if pudendal nerve integrity might have influenced the effects of TMNS (see **"Discussion - Nerve damage"**) a post hoc analysis was conducted. For this purpose, patients were divided into two groups based on the Department of Urology, Herlev Hospital's standards for performing broad resection, which is the operating technique most likely to damage the pudendal nerve. Patients with D'Amico risk classification 1 and 3 were allocated to a narrow resection group and a broad resection group respectively. Patients with D'Amico risk classification 2 were allocated to the

narrow group if they had a Gleason score of 7 (3+4) and to the broad resection group if they had a Gleason score of 7 (4+3). The Wilcoxon signed rank test revealed a statistically significant reduction in the 24-hour pad test in the narrow resection group (n=17) after TMNS with a change of -28 g (-335 to +33 ; p=0.0027). In the broad resection group (n=13) there was no statistically significant reduction in urine loss with a median change of -11 g (-35 to +48 ; p=0.35).

Both groups experienced non-significant decreases in the ICIQ-SF scores immediately after TMNS while no changes were seen after observation (table 8). Regarding IPSS, non-significant decreases in were reported by both groups at week 6 with no subsequent changes at week 12 (table 9). In a pooled analysis of in ICIQ-SF scores from both groups, the improvement reached statistical significance with a change of -1 (-7 to +8 ; p=0.04) between visits before and after TMNS.

Regarding global satisfaction, 18 patients reported to be either very satisfied or partly satisfied (58.1%), 10 patients reported to be neither satisfied nor dissatisfied (32.3%) and 2 patients reported to be either partly dissatisfied or very dissatisfied (6.5%). One patient did not answer the question. Twenty-four patients would recommend TMNS to others (77%). Five would not recommend it and two did not answer the question.

Side effects and unexpected benefits

Out of the original 42 patients in the TMNS group in study 1, five patients experienced side effects: One described red spots on the glans penis while one patient had a small laceration with minimal bleeding. Both of these problems subsided with a break from TMNS for a few days. Two patients described that they became sore while one patient experienced pain in the early postoperative period. The patients who became sore were able to continue therapy, while the patient who experienced pain seized TMNS because of this.

In study 2, 6/39 randomized patients experienced side effects with TMNS. Three patients experienced a few instances of light pain, which did not prevent them from continuing TMNS within the same session. One patient experienced mild bleeding from the glans which resolved within 1 day so that TMNS could be reinitiated. Two patients experienced pain on stimulation, which caused them to discontinue the treatment and withdraw from the study.

This means that the overall incidence of side effects was 11/81 (14%). All side effects were mild and self limiting and no medical treatment was required.

Of interest, five patients in study 2 spontaneously reported an improvement in erectile capacity after TMNS treatment (4 of which had undergone nerve-sparing surgery) and one patient reported to have felt orgasms with TMNS for the first time since his surgery, which took place 645 days before inclusion in the study.

Discussion

General considerations

Nerve-sparing and nerve regeneration are considered crucial components with regard to preservation and restoration of erectile function and urinary continence after RP. Meanwhile, no conservative methods have been able to convincingly ameliorate these problems. The studies in this PhD-thesis represent the first attempts to utilize mechanical nerve stimulation in rehabilitation and treatment of post-prostatectomy functional side effects.

The studies showed that both the idea and the application of TMNS were well accepted by patients. This was seen in the fact that very few patients refused to attempt TMNS and in the high global satisfaction scores in the second study. In addition there were few side effects and the ones we saw were mild and self limiting. This means that the use of TMNS is feasible in clinical practice.

We saw no statistically significant effect of short term penile TMNS applied immediately before and after RP regarding neither erectile function nor urinary continence. Especially the results regarding urinary continence were disappointing. However, the study with early TMNS did show trends toward better erectile function with more potent patients and higher IIEF-5 scores in the treatment group. Here, it is important to note that the variation in individual scores was larger than expected. Considering our power analysis, this means that the study may have included too few patients to detect a significant difference in erectile function between the groups.

The second study showed a potential benefit with TMNS as a treatment for long term manifest UI after RP. Thus, the immediate treatment group experienced reductions in both the 24 hour urine loss as assessed by the pad test and in the number of daily UI episodes. In addition, there was a numerical and borderline-significant improvement on the 24-hour pad test in the delayed treatment group and, importantly, there was a significant reduction in the 24-hour urine loss after TMNS when data from the two groups were pooled. This result implies that the lack of a significant reduction in urine loss with treatment in the delayed treatment group is likely caused by the limited size of our study population. A post hoc analysis revealed that improvements in urinary function were most pronounced in patients were the pudendal nerve was least likely to be damaged. In the study there were also anecdotal reports from some patients that penile TMNS were of benefit to

their erectile and orgasmic functions. This is clearly of additional interest as there are currently limited treatment options for long term ED and as changes in orgasmic sensation are common side effects to RP (89). However, since erectile and orgasmic dysfunctions were not evaluated systematically in the study, the findings should be interpreted with caution and may form the basis of future research.

Taken together the results imply that TMNS may have effects on both long term sexual function and urinary continence after RP in patients with at least some residual nerve function. Considering the proposed mechanism of action of TMNS, this finding seems logical. In this context, our negative results regarding a hastened return to continence with early TMNS are surprising. The lack of effect may be caused by significant differences in preoperative LUTS in the 2 groups. This was shown to be of importance for regaining continence within the study. Preoperative LUTS was also a risk factor for long term UI in a recent case series from Herlev Hospital (paper under peer review). Another possible reason for the discrepancy is that pudendal nerve fibers may need time to recover following surgery before they can be affected by mechanical nerve stimulation.

In spite of the positive signs in both studies, 6 weeks of penile TMNS was certainly unable to ameliorate all erectile and urinary problems. This is clear when considering that only 16/30 patients in the TMNS group regained satisfactory erectile function following surgery and that the median urinary loss in study 2 was approximately cut in half. In addition, the overall reduction in the ICIQ-SF questionnaire in study 2 may be statistically significant, but a median reduction of 1 point must be considered of limited clinical significance. With these findings, our results do not live up to previous results with 6 weeks of TMNS in stress incontinent women, where a remarkable 73% cure rate was seen (81).

Alternative TMNS protocols

The limitations in our results warrant consideration of potential drawbacks to the current TMNS treatment protocol. In this regard, alternative treatment regiments are certainly possible. These include an increase in the duration of the treatment during each session, and an increase in the treatment period. In randomized studies investigating other methods of penile rehabilitation after RP, the treatments have been given for 2-9 months (37-41;44-46) but the optimal length of

treatment is unknown. In studies investigating pelvic floor exercises and other conservative UI treatments, the duration of the therapy varies. However, when utilizing pelvic floor muscle exercises to prevent long term UI, patients are generally instructed to continue training at least until their UI resolves.

In our studies we decided to offer TMNS for a period of 6 weeks, which had yielded positive results in stress incontinent women. When investigating manifest post-prostatectomy UI, this decision seemed logical and straight forward during the design of the study. However, in retrospect, it can be speculated that post surgical UI may be harder to treat and that the duration of treatment should therefore have been increased. With regard to the TMNS treatment immediately following surgery, animal studies have shown that morphological changes in the penile tissue are most pronounced in the early postoperative period (18;21). In addition, patient compliance is known to be poor with long term penile rehabilitation programs (90). Therefore we decided to maintain the relatively short treatment period of TMNS in order to investigate a rehabilitation modality with broad clinical applicability. The only adjustment to the normal 6 week treatment protocol was that our patients were given the device prior to their RP and instructed to begin penile TMNS at least one week before surgery. This was intended to optimize nerve function and to get the participants accustomed to the treatment before they underwent surgery. There is no concrete clinical evidence that these two goals were achieved but it seems highly unlikely that the early treatment would have had detrimental effects.

In retrospect the wisdom of maintaining the 6 week treatment period can be questioned, and a major drawback of our study is the lack of knowledge regarding the possible effects of long term TMNS after RP. Considering the high patient acceptance and compliance with the treatment it would now be obvious to conduct studies of penile TMNS for a period of more than 6 weeks in both the prevention and treatment of functional problems after RP. In addition it would clearly be possible to experiment with longer daily treatment sessions. Likewise, a mode of stimulation where both the ventral and the dorsal side of the glans are stimulated could potentially increase the effect of TMNS as this has been seen with spinal cord injured men when inducing ejaculation (91). This possibility is currently being investigated at Johns Hopkins University, Baltimore, Maryland, USA (clinical trials identifier: NCT01718704). It would also be possible to make adjustments of the vibratory amplitude and frequency. However, when attempting such modifications, it must be kept in mind

that evidence from studies with spinal cord injured men and women with stress UI have shown that high vibratory amplitudes are required to induce a measurable physiological response (75;79;80). In addition to alterations in the TMNS protocol, the effects of TMNS in conjunction with lifestyle advice and PFMT deserve specific investigation as these combinations can readily be employed in clinical practice.

Nerve damage

When considering the two studies, the issue of potential nerve damage during RP warrants discussion. Regarding restoration of erectile function, it is obvious, that at least some residual function of the cavernous nerves must be present for any kind of nerve stimulation to be effective. Since the course of the cavernous nerves is more complex than proposed when nerve sparing was originally described, it is possible the cavernous nerves were not spared in all patients in the study with immediate TMNS after surgery (92). This could be an explanation for the lack of effect in some patients. Another aspect is that, both patients who had undergone surgery with unilateral and bilateral sparing of the cavernous nerves were included in the study. It is well known that, patients who undergo bilateral nerve-sparing generally have the best erectile function following surgery (5). In addition, most of the studies exploring penile rehabilitation programs have looked exclusively at bilaterally nerve spared patients in order to obtain the best results. However, when results from these studies are introduced into clinical practice the distinction between the two types of nerve-sparing tends to disappear. Therefore, both groups of patients were included in our study, in order to explore penile TMNS in the actual clinical setting after RP. In this sense our findings are broadly applicable in clinical practice. The decision can, of course, be criticized as it is possible that there could be a greater effect of TMNS with more rigorous nerve sparing. Conversely, it is possible that patients who undergo unilateral nerve sparing need the rehabilitation the most and will therefore benefit most from nerve stimulation. Although it needs further validation, the concept that patients with a worse prognosis of erectile recovery have the greatest benefit from rehabilitation programs is supported by recent studies. In a non-randomized retrospective study, Gallina and co-authors suggested that penile rehabilitation may only be beneficial in older patients and patients with a diminished preoperative erectile function (93). A similar study by Briganti et al., found that daily PDE5-I treatment showed the best effect in intermediate risk patients (age 66–69 years or IIEF-Erectile Function Domain scores 11–25, Charlson Comorbidity Index ≤1) (94). However, at this

point no general conclusions can be drawn, and certainly no specific conclusions on TMNS are possible. Unfortunately, our study population is too small to perform meaningful sub-analyses regarding effects with different laterality of nerve sparing. The aspect should therefore be explored further in future trials.

In the study with TMNS as a treatment for manifest UI, sparing of the cavernous nerves was not an issue during inclusion as we did not attempt to evaluate erectile function. However, it is quite possible that different degrees of pudendal nerve sparing may have influenced the results. Thus, the integrity of this nerve is crucial in the mechanism of action behind TMNS. This means that structural damage to the pudendal nerve during surgery in some of the participants in our study may have diminished treatment effects. Such nerve damage was not evaluated during surgery and thus we cannot perform a specific analysis on the issue. However, the theory is supported by our post hoc analysis in which we looked at patients based on their likelihood of pudendal nerve damage. This analysis was preformed based on tumor characteristics, where men who had not undergone a wide resection during their RP had the greatest benefit from TMNS. In addition, pudendal nerve damage in some patients may help explain that TMNS was not as effective as in previous studies with women (81). Here, it is likely, that the structural integrity of the pudendal nerves in the female study participants was not disrupted, as none of these had undergone previous surgery. The pudendal nerve aspect could be of importance when attempting TMNS treatment for post-prostatectomy UI in the future. To evaluate this further, the pudendal nerve function could be tested before TMNS for example by investigating the integrity of the bulbocavernosus reflex.

PDE5-inhibitors

With regard to the use of PDE5-I at patient discretion in study 1, we allowed for this possible confounder as our goal was to explore TMNS in the actual clinical setting. Here the reality is that some patients opt for oral medications while others do not. In addition, ethical considerations prompted us to make PDE5-I available as these drugs are a standard treatment following RP with proven efficacy (95). The fact that most patients attempted PDE5-I and the lack of significant differences in drug use between the two groups suggests that it did not influence our results. However, it is possible that there could be a greater effect of TMNS in conjunction with daily use of

PDE5-I. Our sample size does not allow for a sub-analysis to explore this issue but it could be investigated in future trials.

Limitations

The major limitations of both studies in this PhD-thesis are the limited size of the study populations. Thus the standard deviation regarding the IIEF-5 scores in the first study was larger than expected, which means that the study was in effect underpowered. This could be the cause of the lack of a statistically significant difference between groups. In addition there was a somewhat unbalanced dropout from the groups as more patients in the TMNS group were excluded following surgery. The significance of this is unclear, especially since no intention-to-treat analyses were conducted. However, as there were no significant differences regarding patient or tumor parameters between included and excluded participants, it is unlikely to have influenced the results. The second study was not powered to perform a direct comparison between the two study groups, which means that larger studies are needed to confirm the results.

Another obvious limitation in both studies is the lack of placebo treatments. This could especially be a factor in study one, as the outcome measures in this study are subjective. However, as stated above, it was not possible to create a sham intervention due to the nature of the treatment. In addition it can be argued, that any placebo effect of TMNS in the immediate post operative period would likely have faded over time resulting in limited significance at 1 year after surgery.

Conclusion

This PhD-thesis describes the first experience with TMNS in the management of ED and UI after RP. The method proved to be acceptable for most patients and only very few declined to participate in the studies. Side effects were few and mild and patients generally reported to be happy with the treatment. The studies did not document a statistically significant effect of short term TMNS in the 6 week period following surgery and especially the results regarding urinary continence were disappointing. However, there was a trend toward better erectile function in patients who had received TMNS. Conversely, we were able to document statistically significant improvements in urine loss in the group of patients who had continuous problems with UI at least 1 year after surgery. In addition TMNS may have positive effects on erectile function and orgasms in this group.

TMNS is a promising tool in maintaining erectile function following RP and in the treatment of post-prostatectomy UI. However, due to our limited study sizes and the moderate clinical effects, the findings should serve as background for future research rather than as a basis for clinical recommendations at this time. Larger trials are needed to evaluate potential benefits further and to explore alternative treatment protocols with TMNS.

Future perspectives

It is evident that complications to RP will continue to pose a significant problem. Future studies aimed at optimizing functional outcomes following RP are needed. Regarding TMNS, future studies should include investigations with modified stimulation parameters and a longer duration of treatment, both in the immediate post-operative period and when treating manifest UI. In addition, the possible effects on erectile function and orgasms in men who are more than a year after surgery warrants further study. In all studies, it will be important to include control groups because of the possibility of spontaneous recovery of both erectile function and urinary control over time. Future studies should be larger than the current trials, which may be used for power analyses.

In spite of some encouraging findings in the present thesis it is also clear that TMNS does not represent a final solution to the functional side effects of RP. In this regard, methods to reduce nerve damage and trauma during surgery may be the best possibility we have. As I am writing this thesis we are in preparations of exploring such a method at Herlev Hospital. This entails nerve stimulation during robotic surgery to identify the exact location of the pudendal nerves in order to optimize sparing of these structures. In addition I have learned that ED and UI are not the only functional issues facing patients after RP. Many men also experience painful orgasms, reduced orgasmic and penile sensation, reduced penis size and UI specifically associated with sexual activity. These problems may hamper recovery and reduce quality of life and should therefore be addressed. We have evaluated the incidence of the problems (unpublished data) and we are preparing studies, which aim at dealing with these issues. Here, TMNS could potentially play a role.

Reference List

(1) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011 Mar;61(2):69-90.

(2) Quon H, Loblaw A, Nam R. Dramatic increase in prostate cancer cases by 2021. BJU Int 2011 Apr 20.

(3) Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011 Jan;59(1):61-71.

(4) Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2011 May 5;364(18):1708-17.

(5) Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med 2009 Sep;6(9):2538-46.

(6) Krupski TL, Saigal CS, Litwin MS. Variation in continence and potency by definition. J Urol 2003 Oct;170(4 Pt 1):1291-4.

(7) Coelho RF, Rocco B, Patel MB, Orvieto MA, Chauhan S, Ficarra V, et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a critical review of outcomes reported by high-volume centers. J Endourol 2010 Dec;24(12):2003-15.

(8) Johansson E, Steineck G, Holmberg L, Johansson JE, Nyberg T, Ruutu M, et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. Lancet Oncol 2011 Sep;12(9):891-9.

(9) Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. J Urol 1982 Sep;128(3):492-7.

(10) Burnett AL, Tillman SL, Chang TS, Epstein JI, Lowenstein CJ, Bredt DS, et al. Immunohistochemical localization of nitric oxide synthase in the autonomic innervation of the human penis. J Urol 1993 Jul;150(1):73-6.

(11) 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 U S A 2002 Mar;%19;99(6):4061-6.

(12) Borchers H, Brehmer B, Kirschner-Hermanns R, Reineke T, Tietze L, Jakse G. Erectile function after non-nerve-sparing radical prostatectomy: fact or fiction? Urol Int 2006;76(3):213-6.

(13) Masterson TA, Serio AM, Mulhall JP, Vickers AJ, Eastham JA. Modified technique for neurovascular bundle preservation during radical prostatectomy: association between technique and recovery of erectile function. BJU Int 2008 May;101(10):1217-22.

(14) Burnett AL. Rationale for cavernous nerve restorative therapy to preserve erectile function after radical prostatectomy. Urology 2003 Mar;61(3):491-7.

(15) Le JD, Cooperberg MR, Sadetsky N, Hittelman AB, Meng MV, Cowan JE, et al. Changes in specific domains of sexual function and sexual bother after radical prostatectomy. BJU Int 2010 Oct;106(7):1022-9.

(16) Glickman L, Godoy G, Lepor H. Changes in continence and erectile function between 2 and 4 years after radical prostatectomy. J Urol 2009 Feb;181(2):731-5.

(17) 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 Feb;91(2):437-42.

(18) Klein LT, Miller MI, Buttyan R, Raffo AJ, Burchard M, Devris G, et al. Apoptosis in the rat penis after penile denervation. J Urol 1997 Aug;158(2):626-30.

(19) Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. Int J Impot Res 1998 Jun;10(2):113-20.

(20) Mulhall JP, Slovick R, Hotaling J, Aviv N, Valenzuela R, Waters WB, et al. Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. J Urol 2002 Mar;167(3):1371-5.

(21) User HM, Hairston JH, Zelner DJ, McKenna KE, McVary KT. Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. J Urol 2003 Mar;169(3):1175-9.

(22) Leungwattanakij S, Bivalacqua TJ, Usta MF, Yang DY, Hyun JS, Champion HC, et al. Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum. J Androl 2003 Mar;24(2):239-45.

(23) Hu WL, Hu LQ, Song J, Li SW, Zheng XM, Cheng B, et al. Fibrosis of corpus cavernosum in animals following cavernous nerve ablation. Asian J Androl 2004 Jun;6(2):111-6.

(24) Iacono F, Giannella R, Somma P, Manno G, Fusco F, Mirone V. Histological alterations in cavernous tissue after radical prostatectomy. J Urol 2005 May;173(5):1673-6.

(25) Tal R, Teloken P, Mulhall JP. Erectile function rehabilitation after radical prostatectomy: practice patterns among AUA members. J Sex Med 2011 Aug;8(8):2370-6.

(26) Giuliano F, Amar E, Chevallier D, Montaigne O, Joubert JM, Chartier-Kastler E. How urologists manage erectile dysfunction after radical prostatectomy: a national survey (REPAIR) by the French urological association. J Sex Med 2008 Feb;5(2):448-57.

(27) Teloken P, Mesquita G, Montorsi F, Mulhall J. Post-radical prostatectomy pharmacological penile rehabilitation: practice patterns among the international society for sexual medicine practitioners. J Sex Med 2009 Jul;6(7):2032-8.

(28) 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 Jan;20(1):60-7.

(29) Vignozzi L, Filippi S, Morelli A, Ambrosini S, Luconi M, Vannelli GB, et al. Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. J Sex Med 2006 May;3(3):419-31.

(30) Ferrini MG, Davila HH, Kovanecz I, Sanchez SP, Gonzalez-Cadavid NF, Rajfer J. Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat. Urology 2006 Aug;68(2):429-35.

(31) Kovanecz I, Rambhatla A, Ferrini MG, Vernet D, Sanchez S, Rajfer J, et al. Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection. BJU Int 2008 Jan;101(2):203-10.

(32) Lysiak JJ, Yang SK, Klausner AP, Son H, Tuttle JB, Steers WD. Tadalafil increases Akt and extracellular signal-regulated kinase 1/2 activation, and prevents apoptotic cell death in the penis following denervation. J Urol 2008 Feb;179(2):779-85.

(33) 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 May;5(5):1126-36.

(34) 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 Mar;20(2):202-12.

(35) 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 Mar;77(3):761-7.

(36) 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 Apr;8(4):1048-60.

(37) Schwartz EJ, Wong P, Graydon RJ. Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. J Urol 2004 Feb;171(2 Pt 1):771-4.

(38) 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(3):249-52.

(39) 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 Sep;20(5):479-86.

(40) 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 Oct;54(4):924-31.

(41) Aydogdu O, Gokce MI, Burgu B, Baltaci S, Yaman O. Tadalafil rehabilitation therapy preserves penile size after bilateral nerve sparing radical retropubic prostatectomy. Int Braz J Urol 2011 May;37(3):336-44.

(42) Yuan J, Westney OL, Wang R. Design and application of a new rat-specific vacuum erectile device for penile rehabilitation research. J Sex Med 2009 Dec;6(12):3247-53.

(43) Yuan J, Lin H, Li P, Zhang R, Luo A, Berardinelli F, et al. Molecular mechanisms of vacuum therapy in penile rehabilitation: a novel animal study. Eur Urol 2010 Nov;58(5):773-80.

(44) Kohler TS, Pedro R, Hendlin K, Utz W, Ugarte R, Reddy P, et al. A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. BJU Int 2007 Oct;100(4):858-62.

(45) Raina R, Agarwal A, Ausmundson S, Lakin M, Nandipati KC, Montague DK, et al. Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. Int J Impot Res 2006 Jan;18(1):77-81.

(46) Montorsi F, Guazzoni G, Strambi LF, Da Pozzo LF, Nava L, Barbieri L, et al. Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. J Urol 1997 Oct;158(4):1408-10.

(47) Chao R, Mayo ME. Incontinence after radical prostatectomy: detrusor or sphincter causes. J Urol 1995 Jul;154(1):16-8.

(48) Hammerer P, Huland H. Urodynamic evaluation of changes in urinary control after radical retropubic prostatectomy. J Urol 1997 Jan;157(1):233-6.

(49) Shafik A, el-Sherif M, Youssef A, Olfat ES. Surgical anatomy of the pudendal nerve and its clinical implications. Clin Anat 1995;8(2):110-5.

(50) Schraffordt SE, Tjandra JJ, Eizenberg N, Dwyer PL. Anatomy of the pudendal nerve and its terminal branches: a cadaver study. ANZ J Surg 2004 Jan;74(1-2):23-6.

(51) Myers RP, Cahill DR, Kay PA, Camp JJ, Devine RM, King BF, et al. Puboperineales: muscular boundaries of the male urogenital hiatus in 3D from magnetic resonance imaging. J Urol 2000 Oct;164(4):1412-5.

(52) Takenaka A, Murakami G, Matsubara A, Han SH, Fujisawa M. Variation in course of cavernous nerve with special reference to details of topographic relationships near prostatic apex: histologic study using male cadavers. Urology 2005 Jan;65(1):136-42.

(53) Costello AJ, Brooks M, Cole OJ. Anatomical studies of the neurovascular bundle and cavernosal nerves. BJU Int 2004 Nov;94(7):1071-6.

(54) Porena M, Mearini E, Mearini L, Vianello A, Giannantoni A. Voiding dysfunction after radical retropubic prostatectomy: more than external urethral sphincter deficiency. Eur Urol 2007 Jul;52(1):38-45.

(55) Hollabaugh RS, Jr., Dmochowski RR, Kneib TG, Steiner MS. Preservation of putative continence nerves during radical retropubic prostatectomy leads to more rapid return of urinary continence. Urology 1998 Jun;51(6):960-7.

(56) John H, Hauri D. Seminal vesicle-sparing radical prostatectomy: a novel concept to restore early urinary continence. Urology 2000 Jun;55(6):820-4.

(57) Suardi N, Moschini M, Gallina A, Gandaglia G, Abdollah F, Capitanio U, et al. Nerve-sparing approach during radical prostatectomy is strongly associated with the rate of postoperative urinary continence recovery. BJU Int 2013 May;111(5):717-22.

(58) Lucas MG, Bosch RJ, Burkhard FC, Cruz F, Madden TB, Nambiar AK, et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. Eur Urol 2012 Dec;62(6):1130-42.

(59) Campbell SE, Glazener CM, Hunter KF, Cody JD, Moore KN. Conservative management for postprostatectomy urinary incontinence. Cochrane Database Syst Rev 2012;1:CD001843.

(60) Filocamo MT, Li M, V, Del PG, Cecconi F, Marzocco M, Tosto A, et al. Effectiveness of early pelvic floor rehabilitation treatment for post-prostatectomy incontinence. Eur Urol 2005 Nov;48(5):734-8.

(61) Overgard M, Angelsen A, Lydersen S, Morkved S. Does physiotherapist-guided pelvic floor muscle training reduce urinary incontinence after radical prostatectomy? A randomised controlled trial. Eur Urol 2008 Aug;54(2):438-48.

(62) Tienforti D, Sacco E, Marangi F, D'Addessi A, Racioppi M, Gulino G, et al. Efficacy of an assisted low-intensity programme of perioperative pelvic floor muscle training in improving the recovery of continence after radical prostatectomy: a randomized controlled trial. BJU Int 2012 Oct;110(7):1004-10.

(63) Marchiori D, Bertaccini A, Manferrari F, Ferri C, Martorana G. Pelvic floor rehabilitation for continence recovery after radical prostatectomy: role of a personal training re-educational program. Anticancer Res 2010 Feb;30(2):553-6.

(64) Geraerts I, Van PH, Devoogdt N, Joniau S, Van CB, De GA, et al. Influence of Preoperative and Postoperative Pelvic Floor Muscle Training (PFMT) Compared with Postoperative PFMT on Urinary Incontinence After Radical Prostatectomy: A Randomized Controlled Trial. Eur Urol 2013 Jan 21;(13):10.

(65) Centemero A, Rigatti L, Giraudo D, Lazzeri M, Lughezzani G, Zugna D, et al. Preoperative pelvic floor muscle exercise for early continence after radical prostatectomy: a randomised controlled study. Eur Urol 2010 Jun;57(6):1039-43.

(66) Goode PS, Burgio KL, Johnson TM, Clay OJ, Roth DL, Markland AD, et al. Behavioral therapy with or without biofeedback and pelvic floor electrical stimulation for persistent postprostatectomy incontinence: a randomized controlled trial. JAMA 2011 Jan 12;305(2):151-9.

(67) Moore KN, Griffiths D, Hughton A. Urinary incontinence after radical prostatectomy: a randomized controlled trial comparing pelvic muscle exercises with or without electrical stimulation. BJU Int 1999 Jan;83(1):57-65.

(68) Yamanishi T, Mizuno T, Watanabe M, Honda M, Yoshida K. Randomized, placebo controlled study of electrical stimulation with pelvic floor muscle training for severe urinary incontinence after radical prostatectomy. J Urol 2010 Nov;184(5):2007-12.

(69) Mariotti G, Sciarra A, Gentilucci A, Salciccia S, Alfarone A, Di PG, et al. Early recovery of urinary continence after radical prostatectomy using early pelvic floor electrical stimulation and biofeedback associated treatment. J Urol 2009 Apr;181(4):1788-93.

(70) Wille S, Sobottka A, Heidenreich A, Hofmann R. Pelvic floor exercises, electrical stimulation and biofeedback after radical prostatectomy: results of a prospective randomized trial. J Urol 2003 Aug;170(2 Pt 1):490-3.

(71) Laurienzo CE, Sacomani CA, Rodrigues TR, Zequi SC, Guimaraes GC, Lopes A. Results of preoperative electrical stimulation of pelvic floor muscles in the continence status following radical retropubic prostatectomy. Int Braz J Urol 2013 Mar;39(2):182-8.

(72) Yokoyama T, Nishiguchi J, Watanabe T, Nose H, Nozaki K, Fujita O, et al. Comparative study of effects of extracorporeal magnetic innervation versus electrical stimulation for urinary incontinence after radical prostatectomy. Urology 2004 Feb;63(2):264-7.

(73) Terzoni S, Montanari E, Mora C, Ricci C, Destrebecq A. Reducing urine leakage after radical retropubic prostatectomy: pelvic floor exercises, magnetic innervation or no treatment? A quasi-experimental study. Rehabil Nurs 2013 May;38(3):153-60.

(74) Fode M, Krogh-Jespersen S, Brackett NL, Ohl DA, Lynne CM, Sonksen J. Male sexual dysfunction and infertility associated with neurological disorders. Asian J Androl 2012 Jan;14(1):61-8.

(75) Sonksen J, Biering-Sorensen F, Kristensen JK. Ejaculation induced by penile vibratory stimulation in men with spinal cord injuries. The importance of the vibratory amplitude. Paraplegia 1994 Oct;32(10):651-60.

(76) de Groat WC. Integrative control of the lower urinary tract: preclinical perspective. Br J Pharmacol 2006 Feb;147 Suppl 2:S25-S40.

(77) Reitz A, Schmid DM, Curt A, Knapp PA, Schurch B. Afferent fibers of the pudendal nerve modulate sympathetic neurons controlling the bladder neck. Neurourol Urodyn 2003;22(6):597-601.

(78) Farag FF, Martens FM, Rijkhoff NJ, Heesakkers JP. Dorsal genital nerve stimulation in patients with detrusor overactivity: a systematic review. Curr Urol Rep 2012 Oct;13(5):385-8.

(79) Sonksen J, Ohl DA, Wedemeyer G. Sphincteric events during penile vibratory ejaculation and electroejaculation in men with spinal cord injuries. J Urol 2001 Feb;165(2):426-9.

(80) Laessoe L, Sonksen J, Bagi P, Biering-Sorensen F, Ohl DA, McGuire EJ, et al. Effects of ejaculation by penile vibratory stimulation on bladder capacity in men with spinal cord lesions. J Urol 2003 Jun;169(6):2216-9.

(81) Sonksen J, Ohl DA, Bonde B, Laessoe L, McGuire EJ. Transcutaneous mechanical nerve stimulation using perineal vibration: a novel method for the treatment of female stress urinary incontinence. J Urol 2007 Nov;178(5):2025-8.

(82) Sonksen J, Ohl DA, Bonde B, Laessoe L, McGuire EJ. Transcutaneous mechanical nerve stimulation using perineal vibration: a novel method for the treatment of female stress urinary incontinence. J Urol 2007 Nov;178(5):2025-8.

(83) Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol 2010 May;57(5):804-14.

(84) Lucas MG, Bosch RJ, Burkhard FC, Cruz F, Madden TB, Nambiar AK, et al. EAU guidelines on surgical treatment of urinary incontinence. Eur Urol 2012 Dec;62(6):1118-29.

(85) Schou J, Poulsen AL, Nordling J. The value of a new symptom score (DAN-PSS) in diagnosing uro-dynamic infravesical obstruction in BPH. Scand J Urol Nephrol 1993;27(4):489-92.

(86) Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999 Dec;11(6):319-26.

(87) Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn 2004;23(4):322-30.

(88) Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 1992 Nov;148(5):1549-57.

(89) Benson CR, Serefoglu EC, Hellstrom WJ. Sexual dysfunction following radical prostatectomy. J Androl 2012 Nov;33(6):1143-54.

(90) Salonia A, Gallina A, Zanni G, Briganti A, Deho F, Sacca A, et al. Acceptance of and discontinuation rate from erectile dysfunction oral treatment in patients following bilateral nerve-sparing radical prostatectomy. Eur Urol 2008 Mar;53(3):564-70.

(91) Brackett NL, Kafetsoulis A, Ibrahim E, Aballa TC, Lynne CM. Application of 2 vibrators salvages ejaculatory failures to 1 vibrator during penile vibratory stimulation in men with spinal cord injuries. J Urol 2007 Feb;177(2):660-3.

(92) 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 Feb;57(2):179-92.

(93) Gallina A, Ferrari M, Suardi N, Capitanio U, Abdollah F, Tutolo M, et al. Erectile function outcome after bilateral nerve sparing radical prostatectomy: which patients may be left untreated? J Sex Med 2012 Mar;9(3):903-8.

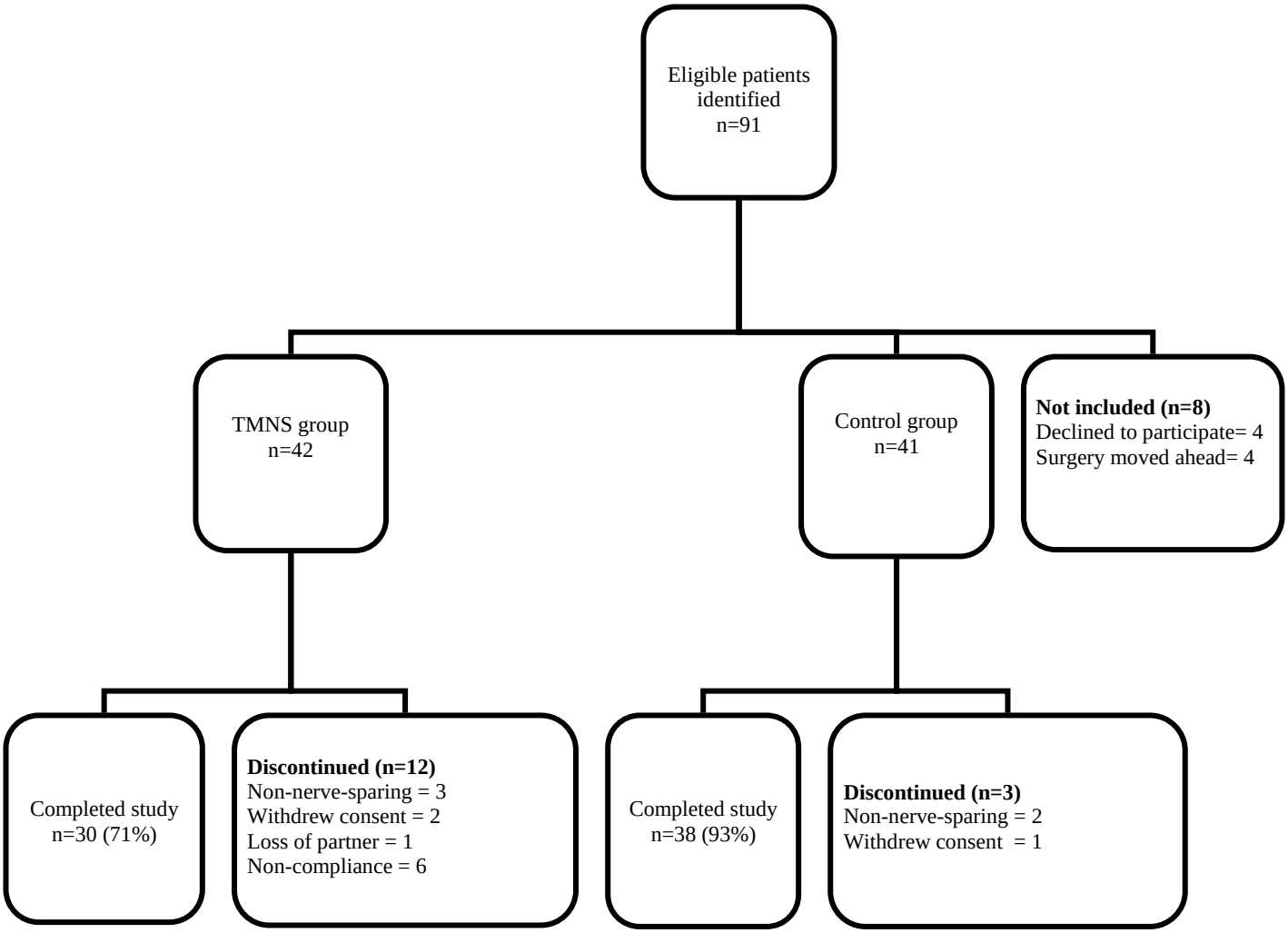
(94) Briganti A, Di TE, Abdollah F, Gallina A, Suardi N, Capitanio U, et al. Choosing the best candidates for penile rehabilitation after bilateral nerve-sparing radical prostatectomy. J Sex Med 2012 Feb;9(2):608-17.

(95) Miles CL, Candy B, Jones L, Williams R, Tookman A, King M. Interventions for sexual dysfunction following treatments for cancer. Cochrane Database Syst Rev 2007;(4):CD005540.

Figure 1: The FERTI CARE® vibrator (Multicept A/S, Frederiksberg, Denmark).

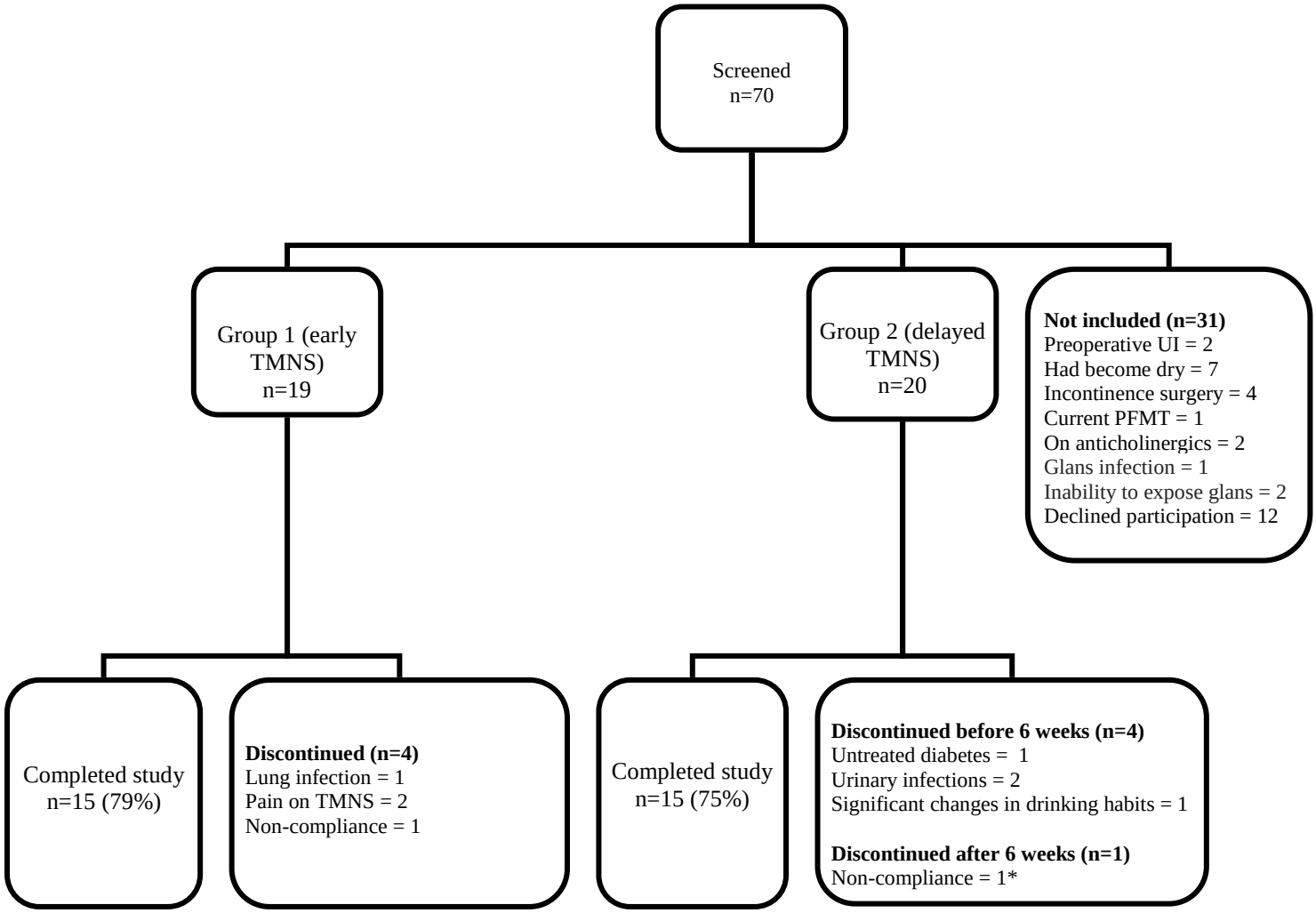
The device was set to an amplitude of 2 mm and a vibration frequency of 100 Hz in both studies. Patients were instructed in stimulating the frenulum once daily with a sequence consisting of 10 seconds of stimulation followed by a 10 second pause repeated 10 times (for a total of 100 seconds of stimulation every day).

Figure 2: The flow of patients in study 1



TMNS: Transcutaneous mechanical nerve stimulation

Figure 3: The flow of patients in study 2



TMNS: Transcutaneous mechanical nerve stimulation

PFMT: Pelvic floor muscle training

*The patient who discontinued the study after the first 6 weeks is included in the 6-week analyses.

Table 1: Patient characteristics in study 1

	Median age (years)	Nerve-sparing	Robot-assisted surgery	Preoperative IIEF-5 score (median (range))	Preoperative DAN-PSS score (median (range))	Proportion of patients using postoperative PDE5-inhibitors
TMNS	62 (46-73)	Bilateral: 19 Unilateral: 11	Yes: 27 No: 3	25 (19–25)	3.5 (0-27)	3 months: 9/30 6 months: 19/30 12 months: 17/30
Control	65 (49-76)	Bilateral: 18 Unilateral: 20	Yes: 34 No: 4	25 (18-25)	2 (0-20)	3 months: 17/38 6 months: 25/38 6 months: 19/38
p-value	0.095	0.23	0.99	0.68	0.048	3 months: 0.16 6 months: 0.72 12 months: 0.58

DAN-PSS: Danish Prostate symptom score

IIEF-5: International Index of Erectile Function-5

PDE5-I: PDE5-inhibitors

TMNS: Transcutaneous mechanical nerve stimulation

Table 2: Tumor characteristics in study 1

	Pathological tumor stage	Pathological Gleason score	Prostate volume (ml) (median (range))	Preoperative PSA (ng/ml) (median (range))
TMNS	T2a: 2 T2b: 3 T2c: 16 T3a: 7 T3b: 1 T4 : 1	Gleason 5: 1 Gleason 6: 10 Gleason 7: 18 Gleason 8: 0 Gleason 9: 1	49 (21-165)	7.1 (0.7-20)
Control	T2a: 3 T2b: 1 T2c: 20 T3a: 12 T3b: 2 T4 : 0	Gleason 5: 1 Gleason 6: 6 Gleason 7: 24 Gleason 8: 5 Gleason 9: 2	51 (28-138)	7.45 (0.6-20)
p-value	0.70	0.23	0.77	0.65

PSA: Prostate-specific antigen

Table 3: Erectile function outcomes in the two groups after RP. IIEF-5 scores are given as medians (range). Number of patients with IIEF-5 scores ≥ 18 are given as proportions (%).

	IIEF-5 at 3 months	IIEF-5 at 6 months	IIEF-5 at 12 months	IIEF-5 ≥ 18 at 3 months	IIEF-5 ≥ 18 at 6 months	IIEF-5 ≥ 18 at 12 months
TMNS	5 (0-25)	10.5 (0-25)	18 (0-25)	5/30 (17%)	13/30 (43%)	16/30 (53%)
Control	5 (0-25)	5 (0-25)	7.5 (0-25)	4/38 (11%)	9/38 (24%)	12/38 (32%)
p-value	0.25	0.08	0.09	0.46	0.09	0.07

TMNS: Transcoutaneous mechanical nerve stimulation

IIEF-5: International Index of Erectile Function-5

Table 4: Continence rates (%) and pad use (median (range)) after radical prostatectomy

	Continence at 3 months	Continence at 6 months	Continence at 12 months	Pad use at 3 months	Pad use at 6 months	Pad use at 12 months
TMNS	65.5	83.3	90	1 (0 - 6)	0 (0 - 3)	0 (0 - 2)
Control	62.9	91.9	94.7	1 (0 - 4)	1/3 (0 - 6)*	0 (0 - 3)
p-value	0.83	0.28	0.46	0.09	0.14	0.56

TMNS: Transcutaneous mechanical nerve stimulation

*One patient reported to use 1/3 of a pad daily. As there was no pre-specified decision on how to deal with such reporting, it was taken for face-value when analysing the results.

Table 5: DAN-PSS (median and range) after radical prostatectomy in study 1

	3 months	6 months	12 months
TMNS	3 (0-34)	2 (0-41)	3 (0-36)
Control	5 (0-34)	1 (0-48)	0.5 (0-21)
p-value	0.74	0.74	0.13

DAN-PSS: Danish Prostate symptom score

TMNS: Transcutaneous mechanical nerve stimulation

Table 6: Baseline patient characteristics in study 2

	Age in years (median (range))	Nerve-sparing	Robot-assisted surgery	Amount of urine loss per 24 hours (g) (median (range))	Number of incontinence episodes per 24 hours (median (range)	IPSS (median (range))	ICIQ-SF score (median (range))	Time since surgery (months) (median (range))
Group 1	67 (61-76)	Yes: 9 No: 6	Yes: 9 No: 6	60 (13–683)	4 (0.3-14)	9 (1-18)	13 (7-21)	593 (397-1188)
Group 2	67 (51-74)	Yes: 8 No: 8	Yes: 11 No: 5	41 (8-400)	4.2 (1-13.7)	9.5 (3-25)	14 (9-20)	573.5 (393-1313)
p-value	0.73	0.58	0.61	0.65	0.42	0.61	0.75	0.95

ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form

IPSS: International Prostate Symptom Score

Table 7: Tumor characteristics in study 2

	Clinical tumor stage	Biopsy Gleason score	Preoperative PSA (ng/ml) (median (range))	Pathological tumor stage	Pathological Gleason score
Group 1	T1: 8 T2a: 1 T2b: 5 T2c: 1	Gleason 6: 3 Gleason 7: 10 Gleason 8: 2 Gleason 9: 0	8 (0.3-25)	T2a: 1 T2b: 1 T2c: 11 T3a: 2 T3b: 0	Gleason 5: 1 Gleason 6: 2 Gleason 7: 11 Gleason 8: 1 Gleason 9: 0
Group 2	T1: 6 T2a: 3 T2b: 4 T2c: 3	Gleason 6: 1 Gleason 7: 11 Gleason 8: 2 Gleason 9: 2	7 (5-20)	T2a: 0 T2b: 0 T2c: 9 T3a: 6 T3b: 1	Gleason 5: 0 Gleason 6: 2 Gleason 7: 11 Gleason 8: 2 Gleason 9: 1
p-value	0.59	0.68	0.81	0.22	0.99

PSA: Prostate-specific antigen

Table 8: ICIQ-SF score changes throughout study 2 (median (range))

ICIQ-SF score change	Group 1	Group 2
Baseline to week 6	- 2 (-6 to +8), p=0.18	+ 0.5 (-5 to +5), p=0.93
Week 6 to week 12	0 (-3 to +7), p=0.93	- 1 (-7 to +2), p=0.23

ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form

Table 9: IPSS score changes throughout study 2 (median (range))

IPSS change	Group 1	Group 2
Baseline to week 6	- 1 (-8 to +7), p=0.49	- 1.5 (-6 to +5), p=0.27
Week 6 to week 12	0 (-7 to +4), p=0.46	0 (-8 to +5), p=0.92

IPSS: International Prostate Symptom Score

Penile vibratory stimulation in the preservation and restoration of urinary continence and erectile function in conjunction with nerve sparing radical prostatectomy: A randomized, controlled trial

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Abstract

Objective: To examine the effect of penile vibratory stimulation (PVS) in the preservation and restoration of erectile function and urinary continence in conjunction with nerve-sparing radical prostatectomy.

Subjects/patients and methods: The study was conducted between July 2010 and March 2013 as a randomized prospective trial at two university hospitals. Eligible participants were continent men with an International Index of Erectile Function-5 (IIEF-5) score of at least 18, scheduled to undergo nerve sparing radical prostatectomy.

Patients were randomized to a PVS group or a control group. Patients in the PVS group were instructed in using a PVS device (FERTI CARE® vibrator, Multicept A/S, Frederiksberg,

Denmark). Stimulation was performed at the frenulum once daily by the patients in their own homes for a minimum of one week prior to surgery. After catheter removal, daily PVS was re-initiated for a period of six weeks. Participants were evaluated at 3, 6 and 12 months following surgery with the IIEF-5 questionnaire and questions regarding urinary bother. Patients useing up to 1 pad daily for security reasons only were considered continent. The study was registered at www.clinicaltrials.org (NCT01067261).

Results: Data from 68 patients were available for analyses (30 patients randomized to PVS and 38 patients randomized to the control group). The IIEF-5 score was highest in the PVS group at all time points after surgery with a median score of 18 vs. 7.5 in the control group at 12 months (p=0.09), but the difference only reached borderline significance. At 12 months 16/30 (53%) patients in the PVS group had reached an IIEF-5 score of at least 18 while this was the case for 12/38 (32%) patients in the control group (P=0.07). There were no significant differences in the proportions of continent patients between groups at either 3, 6 or 12 months. At 12 months 90% of the PVS patients were continent while 94.7% of the control patients were continent (P=0.46).

Conclusion: Our study did not document significant effect of PVS. However, the method proved to be acceptable for most patients and there was a trend toward better erectile function with PVS. More studies are needed to explore this possible effect further.

Key words

Erectile dysfunction, nerve sparing surgery, penile rehabilitation, penile vibratory stimulation, prostate cancer, radical prostatectomy, urinary incontinence.

Introduction

Radical prostatectomy (RP) is a commonly employed treatment for localized prostate cancer. Unfortunately, a substantial part of the patients will experience adverse effects in the form of urinary incontinence and erectile dysfunction (ED) after the surgery [1]. The cavernous nerves are responsible for inducing normal erections, and as these nerves run in close proximity to the prostate gland they are in danger of being damaged during RP. Thus, it is well accepted that the main pathophysiological mechanism behind post-prostatectomy ED is damage to the cavernous nerves. To improve erectile function after surgery, nerve sparing procedures have therefore been developed and whenever tumor characteristics allow it, these are routinely employed [2]. However, even when the cavernous nerves are left anatomically intact, it is likely that they are affected by mechanical manipulation, heating, ischemic effects, and local inflammation [3,4]. This is believed to cause neuropraxia, defined as a temporary block of nerve transmission despite an anatomical intact nerve fiber. Postoperative incontinence can be caused by damage to the urinary sphincter and changes in the course of the urethra after surgery. However incontinence may also occur if these structures are not compromised, which may be connected to changes in the closing pressure of the urinary sphincter and sometimes reduced bladder capacity [5]. In these cases it is likely that nerve damage plays a pathophysiological role. Rehabilitation of patients' sexual function is often attempted with various regiments of PDE5-inhibitors, vacuum erection devices and/or injection therapy [6-8]. Meanwhile rehabilitation regarding urinary continence is routinely performed by instructing patients in pelvic floor exercises before or after their surgery. Unfortunately, these rehabilitation attempts are often unsuccessful and new methods are needed [9,10]. One possible reason that current methods have generally shown disappointing results in preserving erectile function and continence is that they do not target the pelvic nerves.

It has previously been shown that one can stimulate the nerves of the pelvic floor by means of penile vibratory stimulation (PVS) [11-13]. Therefore it is feasible that this method can improve nerve function and thereby prevent or minimize the occurrence of incontinence and erectile dysfunction following pelvic surgery. The purpose of the present study is to examine the effect of PVS in the preservation and restoration of erectile function and urinary continence in conjunction with radical prostatectomy.

Subjects/patients and methods

The study was conducted between July 2010 and March 2013 as a randomized controlled trial at two university hospitals. Eligible participants were men scheduled to undergo nerve sparing RP. Only men who were sexually active with an International Index of Erectile Function-5 (IIEF-5) [15] score of at least 18 without erectogenic aids, and fully continent before surgery (as assessed by the validated Danish Prostate symptom score (DAN-PSS), were included in the study. The DAN-PSS is a patient administered questionnaire based on 12 symptoms related to bladder storage and voiding function and describes both the severity and the perceived bother related to each symptom [14]. In order to maintain a uniform patient group, exclusion criteria included any condition which would prevent the participant from attempting post operative treatment with a PDE5-inhibitor.

Data regarding preoperative erectile function (assessed by the IIEF-5 questionnaire), and preoperative LUTS (assessed by the DAN-PSS questionnaire) were collected at inclusion. Eligible patients were then randomized by a draw using opaque envelopes to either a PVS group or a control group. In both groups the patients received one preoperative session with pelvic floor muscle training instruction. In addition, patients in the PVS group were instructed

in using a PVS device (FERTI CARE® vibrator, Multicept A/S, Frederiksberg, Denmark) during the same session (figure 1). The device was set to an amplitude of 2 mm and a vibration frequency of 100 Hz. Patients were instructed in stimulating the frenulum once daily with a sequence consisting of 10 seconds of stimulation followed by a 10 second pause repeated 10 times (for a total of 100 seconds of stimulation every day). The patients were given a FERTI CARE® vibrator to use daily in their homes for a minimum of one week prior to surgery. In conjunction with surgery, the laterality of nerve sparing (unilateral/bilateral) was noted based on the assessment of the surgeon and patients who underwent a non-nerve-sparing procedure were excluded at this point. Following the surgery, remaining participants in the PVS group were instructed to re-initiate the stimulation at catheter removal and continue daily stimulation for a period of six weeks. All participants in both groups were contacted by phone to ensure compliance with pelvic floor exercises and PVS at two and six weeks following surgery. At these contacts patients in the PVS group were asked systematically about side effects to the treatment. In both groups the patients were offered on-demand or daily PDE5-inhibitor treatment at one month following surgery.

Participants were evaluated at 3, 6 and 12 months following surgery with the IIEF-5 questionnaire for erectile function and DAN-PSS for urinary bother. In addition patients were asked to rate their continence and to report their use of pads/diapers at each visit. Patients reporting to use up to 1 pad daily for security reasons only were considered continent.
The primary end point regarding erectile function was the difference in median IIEF-5 score between the groups. The primary endpoint regarding continence was time to continence following surgery. Secondary outcome measures included the number of patients who had achieved an IIEF-5 score of at least 18 with or without PDE5-inhibitors at 3, 6 and 12 months

following surgery as well as the overall difference in reported pad use and the difference in postoperative DAN-PSS.

The sample size was calculated based on the IIEF-5 questionnaire. With a two sided significance level set at 0.05 it was calculated that 64 patients would be needed to detect a minimally clinically meaningful difference of 5 with a standard deviation of 6 and a power of 80%. To account for subsequent exclusion, drop out and anticipated non compliance we aimed at including 80 patients in the pre-operative phase.

The Wilcoxon-Mann-Whitney test was used to assess differences in continuous parameters while Fisher's exact test or the chi squared test was used to compare groups with regard to categorical variables. Outcome measures are presented as percentages or as medians and range. All statistical tests were performed with the SAS version 9.2 statistical software package for windows (Institute Inc., Cary, NC, USA). The study was approved by the Danish ethical counsel and the Danish Data Protection Agency. It was registered at www.clinicaltrials.org (NCT01067261).

Results

A total of 91 eligible patients were identified and asked to participate in the study. and 83 patients were included preoperatively (42 randomized to the PVS group and 41 randomized to the control group). In total, data from 68 patients were available for analysis (30 patients randomized to vibration therapy and 38 patients randomized to the control group). Reasons for exclusion included non-nerve-sparing surgery (n=5), withdrawn consent (n=3), loss of partner (n=1) and non-compliance with the PVS protocol (n=6). Of the 6 non-compliant patients, 4 could not use the device post-operatively because they had a catheter in place for

an extended period of time while one felt pain on vibration. The last patient stated that he did not feel comfortable with PVS. The flow of patients is illustrated in figure 2.

There were no statistically significant differences in age, degree of nerve sparing, robotic/open surgery, preoperative IIEF-5 score or postoperative use of PDE5-inhibitors between the groups, however, patients randomized to the PVS group had significantly more LUTS prior to surgery (p= 0.048) (table 1). There were no significant differences in tumor stage (p= 0.7), Gleason score (p=0.19) or preoperative PSA (p=0.66) between groups. Likewise, there were no statistically significant differences regarding any of the mentioned parameters between the final 68 patients and the 10 patients who were excluded for reasons other than a lack of nerve sparing. Follow-up data was available for 64/68 patients at 3 months, 67/68 patients at 6 months and 68/68 patients at 12 months.

The IIEF-5 score was higher in the PVS group at all time points after surgery but the difference between groups only reached borderline significance with a median score of 18 (0-25) in the PVS group vs. 7.5 (0-25) in the control group at 12 months (table 2). At 12 months post surgery 16/30 (53%) patients in the PVS group had reached an IIEF-5 score of at least 18 while this was the case for 12/38 (32%) patients in the control group (P=0.07). There was also a non-significant trend toward more men returning to an IIEF score of at least 18 at 6 months (p=0.09) while there was no difference in potency rates 3 months after surgery (p=0.46).

There were no significant differences in the proportions of continent patients between groups at either 3, 6 or 12 months after surgery (table 3). At 12 months 90% of the PVS patients were continent while 94.7% of the control patients were continent (P=0.46). There was a non-significant trend toward a higher number of pads in the PVS group at 3 months while there were no differences at 6 and 12 months (table 3). Likewise, there were no significant

differences between groups in total DAN-PSS between groups at any point after the surgery (table 4).

Due to the skewed preoperative DAN-PSS between the two groups, post hoc analyses were conducted to assess if the preoperative DAN-PSS was associated to urinary outcomes. These analyses showed that a high preoperative score was associated with incontinence at 12 months ($p= 0.035$) and with postoperative DAN-PSS at all time points during follow up.Out of the original 42 patients in the PVS group, five experienced side effects related to the PVS. One described red spots on the glans penis while one patient had a small laceration with minimal bleeding. In addition two patients described that they became sore while one patient experienced frank pain in the early postoperative period. All side effects were self limiting and no medical treatment was required. However, as stated above, the patient who experienced pain seized PVS because of this.

Discussion

Nerve-sparing and nerve regeneration are believed to be key components with regard to post prostatectomy functional outcomes and our study represents the first attempt to utilize nerve stimulation in a rehabilitation program. The neuroanatomical background is that afferent nerve fibers from the glans penis run through the dorsal penile nerve to join with fibers from the the pudendal nerve [16,17]. Through this they reach the spinal cord at the spinal levels S2-S4 [16,17]. Conversely, parasympathetic fibers from S2-S4 in the spinal cord constitute the efferent limb of the erectile response via the cavernous nerve while somatic fibers running through the pudendal nerve innervate the pelvic floor muscles and the external urinary sphincter. Meanwhile afferent nerves from the penis also reach the sympathetic center in the

thoracolumbar part of the spinal cord where they may affect bladder contractility [18-20]. Possibly working through these pathways, studies have identified several potential benefits from genital and perineal PVS, including ejaculation and reduction of bladder overactivity in spinal cord injured men and an improvement in stress incontinence in women [12,13,19]. The first hypothesis of the current study was that PVS in the early post operative period after RP can stimulate the cavernous nerves through the described reflex arch and aid in the restitution from neuropraxia. This could in turn improve long term erectile function. The second hypothesis was that PVS could improve urinary control through improved ability to contract the pelvic floor muscles and the external urinary sphincter. Unfortunately we were unable to identify a significant effect of 6 weeks of PVS following radical prostatectomy as assessed by our primary outcome measures. Especially the results regarding urinary continence were disappointing. However, the study does show that the method is acceptable to patients and that side effects are limited. In addition the trends toward better erectile function in the treatment group imply that PVS may have some effect on long term erectile function.

The stimulation parameters in our study were chosen based on previous research regarding urinary incontinence in women [13] and on clinical data from treating post-prostatectomy incontinence with PVS at our center (unpublished data). As knowledge from animal studies indicate that penile changes are most pronounced in the early postoperative period [21,22] and as patient compliance with long term penile rehabilitation programs is known to be poor [23], we decided to maintain the relatively short treatment duration of 6 weeks following catheter removal. The only adjustment to the previous PVS protocol was that participants were instructed to begin treatment at least one week before surgery. This was a pragmatic decision, which was intended partly to optimize nerve function before surgery and partly to get the patients used to the PVS device. Our protocol meant that vibratory stimulation was stopped

approximately two months after surgery. Admittedly the wisdom of this decision can be questioned in retrospect as a major drawback of our study is the lack of data regarding effects of long term PVS after RP. However, our focus was to investigate a rehabilitation modality with broad clinical applicability. Considering the patient acceptance it would now be obvious to initiate studies of PVS extended for a period of more than 6 weeks in post prostatectomy sexual rehabilitation and to experiment with longer daily treatment sessions.

With regard to the clinical applicability, the inclusion of both unilaterally nerve spared and bilaterally nerve spared patients and the broad use of PDE5-I warrant discussion. We allowed for these possible confounders in the design of the study as we wanted to explore PVS in the actual clinical setting after a radical prostatectomy. Furthermore, ethical considerations prevented us from denying participant from PDE5-I following surgery since these drugs have been shown to be effective in this setting while effects of PVS were unknown [24]. The lack of significant differences in the two parameters between the two groups suggests that it did not influence our results. However, it is possible that there could be a greater effect of PVS with more rigorous nerve sparing and that the effect could be modified with daily administration of PDE5-I. Unfortunately, our sample size does not allow for meaningful post hoc analysis to explore these issues.

Regarding the costs of PVS with the FERTI CARE® vibrator, each machine costs approximately € 500 while the disposable plastic discs (see figure 1) cost about € 5 a piece. The device can be cleaned and sterilized between patients and can thus be reused several times. In the authors' experience there is no set maximum number of times a device can be reused. However the battery time goes down over time and patients may break the device for example by dropping it or by bringing it into the shower. One disc is sufficient for each

patient as there is no significant wear on these. However, they are disposed of between patients for hygienic reasons.

Our study is the first of its kind and while this must be considered a significant strength, the study is not without weaknesses. Patients randomized to the PVS group had significantly more LUTS prior to surgery compared to the no-treatment group. Subsequent analyses revealed that this likely impacted postoperative urinary function making the results our study questionable regarding this outcome. It is also worthy of consideration that our standard deviation was larger than expected. This means that the study population may have been too small to show a significant difference between the groups regarding erectile function. The trend toward more potent patients and higher IIEF-5 score in the PVS group implies that this could be the case.

While post prostatectomy PVS cannot be recommended based on our results, the borderline significant results of our study certainly justifies further research in the area. In this regard it is obvious that alternative treatment regiments are possible. In addition to an increase in the duration of the treatment, modifications to the treatment protocol should be considered. As speculated in a recent review paper, a mode of stimulation where both the ventral and the dorsal side of the glans is stimulated could potentially increase effect as this has been seen with spinal cord injured men [25]. Other modifications may include adjustments of the vibratory amplitude and frequency. However, it must be cautioned that experience from other patient groups suggest that the relatively high amplitude employed in our study is required to induce a physiological response.

We report the first experience with PVS in preservation and restoration of post-prostatectomy erectile function and incontinence. Our study did not document significant effect of 6 weeks of postoperative PVS. However, the method proved to be acceptable for most patients and

there was a trend toward better erectile function in patients who had undergone PVS. More studies are needed to explore this possible effect further. In this regard, future research should attempt to make adjustments in the PVS protocol.

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References

1 Penson DF, McLerran D, Feng Z, Li L, Albertsen PC, Gilliland FD et al. 5-year urinary and sexual outcomes after radical prostatectomy: results from the Prostate Cancer Outcomes Study. *J Urol* 2008: **179**(5 Suppl):S40-S44.

2 Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. *J Urol* 1982: **128**(3):492-497.

3 Masterson TA, Serio AM, Mulhall JP, Vickers AJ, Eastham JA. Modified technique for neurovascular bundle preservation during radical prostatectomy: association between technique and recovery of erectile function. *BJU Int* 2008: **101**(10):1217-1222.

4 Burnett AL. Rationale for cavernous nerve restorative therapy to preserve erectile function after radical prostatectomy. *Urology* 2003: **61**(3):491-497.

5 Hammerer P, Huland H. Urodynamic evaluation of changes in urinary control after radical retropubic prostatectomy. *J Urol* 1997: **157**(1):233-236.

6 Tal R, Teloken P, Mulhall JP. Erectile function rehabilitation after radical prostatectomy: practice patterns among AUA members. *J Sex Med* 2011: **8**(8):2370-2376.

7 Giuliano F, Amar E, Chevallier D, Montaigne O, Joubert JM, Chartier-Kastler E. How urologists manage erectile dysfunction after radical prostatectomy: a national survey (REPAIR) by the French urological association. *J Sex Med* 2008: **5**(2):448-457.

8 Teloken P, Mesquita G, Montorsi F, Mulhall J. Post-radical prostatectomy pharmacological penile rehabilitation: practice patterns among the international society for sexual medicine practitioners. *J Sex Med* 2009: **6**(7):2032-2038.

9 Campbell SE, Glazener CM, Hunter KF, Cody JD, Moore KN. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev* 2012: **1**:CD001843.

10 Fode M, Ohl D, Ralph D, Sønksen J. Penile Rehabilitation after Radical Prostatectomy: What the Evidence Really Says. *BJU Int* 2013: **doi: 10.1111/bju.12228**.

11 Sonksen J, Biering-Sorensen F, Kristensen JK. Ejaculation induced by penile vibratory stimulation in men with spinal cord injuries. The importance of the vibratory amplitude. *Paraplegia* 1994: **32**(10):651-660.

12 Sonksen J, Ohl DA, Wedemeyer G. Sphincteric events during penile vibratory ejaculation and electroejaculation in men with spinal cord injuries. *J Urol* 2001: **165**(2):426-429.

13 Sonksen J, Ohl DA, Bonde B, Laessoe L, McGuire EJ. Transcutaneous mechanical nerve stimulation using perineal vibration: a novel method for the treatment of female stress urinary incontinence. *J Urol* 2007: **178**(5):2025-2028.

14 Schou J, Poulsen AL, Nordling J. The value of a new symptom score (DAN-PSS) in diagnosing uro-dynamic infravesical obstruction in BPH. *Scand J Urol Nephrol* 1993: **27**(4):489-492.

15 Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999: **11**(6):319-326.

16 Shafik A, el-Sherif M, Youssef A, Olfat ES. Surgical anatomy of the pudendal nerve and its clinical implications. *Clin Anat* 1995: **8**(2):110-115.

17 Schraffordt SE, Tjandra JJ, Eizenberg N, Dwyer PL. Anatomy of the pudendal nerve and its terminal branches: a cadaver study. *ANZ J Surg* 2004: **74**(1-2):23-26.

18 Reitz A, Schmid DM, Curt A, Knapp PA, Schurch B. Afferent fibers of the pudendal nerve modulate sympathetic neurons controlling the bladder neck. *Neurourol Urodyn* 2003: **22**(6):597-601.

19 Laessoe L, Sonksen J, Bagi P, Biering-Sorensen F, Ohl DA, McGuire EJ et al. Effects of ejaculation by penile vibratory stimulation on bladder reflex activity in a spinal cord injured man. *J Urol* 2001: **166**(2):627.

20 Farag FF, Martens FM, Rijkhoff NJ, Heesakkers JP. Dorsal genital nerve stimulation in patients with detrusor overactivity: a systematic review. *Curr Urol Rep* 2012: **13**(5):385-388.

21 Klein LT, Miller MI, Buttyan R, Raffo AJ, Burchard M, Devris G et al. Apoptosis in the rat penis after penile denervation. *J Urol* 1997: **158**(2):626-630.

22 User HM, Hairston JH, Zelner DJ, McKenna KE, McVary KT. Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. *J Urol* 2003: **169**(3):1175-1179.

23 Salonia A, Gallina A, Zanni G, Briganti A, Deho F, Sacca A et al. Acceptance of and discontinuation rate from erectile dysfunction oral treatment in patients following bilateral nerve-sparing radical prostatectomy. *Eur Urol* 2008: **53**(3):564-570.

24 Miles CL, Candy B, Jones L, Williams R, Tookman A, King M. Interventions for sexual dysfunction following treatments for cancer. *Cochrane Database Syst Rev* 2007:(4):CD005540.

25 Tajkarimi K, Burnett AL. The role of genital nerve afferents in the physiology of the sexual response and pelvic floor function. *J Sex Med* 2011: **8**(5):1299-1312.

Figure 1: The FERTI CARE® vibrator. The vibratory stimulation of the device is delivered through a reusable but disposable black plastic disc as seen on the right end of the picture. The device was set to an amplitude of 2 mm and a vibration frequency of 100 Hz. Patients were instructed in stimulating the frenulum once daily with a sequence consisting of 10 seconds of stimulation followed by a 10 second pause repeated 10 times (for a total of 100 seconds of stimulation every day).

Figure 2: The flow of patients throughout the study

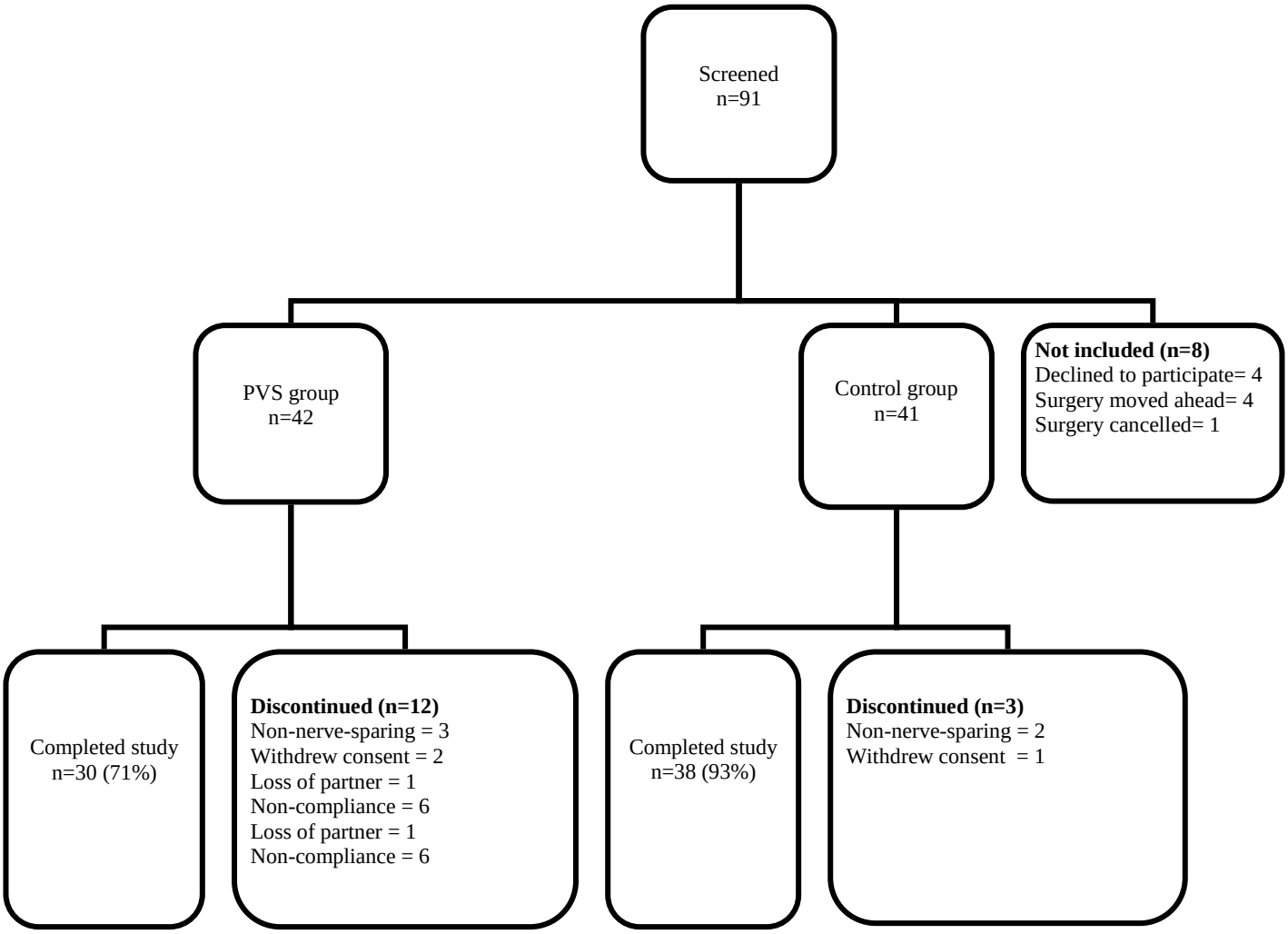

Table 1: Patient characteristics

	Median age (years)	Nerve-sparing	Robot-assisted surgery	Preoperative IIEF-5 score	Preoperative DAN-PSS score	Proportion of patients using postoperative PDE5-inhibitors
PVS	62 (46-73)	Bilateral: 19 Unilateral: 11	Yes: 27 No: 3	25 (19–25)	3.5 (0-27)	3 months: 9/30 6 months: 19/30 12 months: 17/30
Control	65 (49-76)	Bilateral: 18 Unilateral: 20	Yes: 34 No: 4	25 (18-25)	2 (0-20)	3 months: 17/38 6 months: 25/38 6 months: 19/38
p-value	0.095	0.23	0.99	0.68	0.048	3 months: 0.16 6 months: 0.72 12 months: 0.58

Table 2: Erectile function outcomes in the two groups after RP

	IIEF-5 at 3 months	IIEF-5 at 6 months	IIEF-5 at 12 months	IIEF-5 ≥ 18 at 3 months	IIEF-5 ≥ 18 at 6 months	IIEF-5 ≥ 18 at 12 months
PVS	5 (0-25)	10.5 (0-25)	18 (0-25)	5/30 (17%)	13/30 (43%)	16/30 (53%)
Control	5 (0-25)	5 (0-25)	7.5 (0-25)	4/38 (11%)	9/38 (24%)	12/38 (32%)
p-value	0.25	0.08	0.09	0.46	0.09	0.07

Table 3: Continence rates and pad use (median and range) after surgery

	Continence at 3 months	Continence at 6 months	Continence at 12 months	Pad use at 3 months	Pad use at 6 months	Pad use at 12 months
PVS	65.5%	83.3%	90%	1 (0 - 6)	0 (0 - 3)	0 (0 - 2)
Control	62.9%	91.9%	94.7%	1 (0 - 4)	1/3 (0 - 6)*	0 (0 - 3)
p-value	0.83	0.28	0.46	0.09	0.14	0.56

*One patient reported to use 1/3 of a pad daily. As there was no pre-specified decision on how to deal with such reporting, it was taken for face-value when analysing the results.

Table 4: DAN-PSS (median and range) after surgery

	3 months	6 months	12 months
PVS	3 (0-34)	2 (0-41)	3 (0-36)
Control	5 (0-34)	1 (0-48)	0.5 (0-21)
p-value	0.74	0.74	0.13

Penile vibratory stimulation in the treatment of post-prostatectomy incontinence: A randomized pilot study

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Abstract

Objective: To examine the effects of penile vibratory stimulation (PVS) in the treatment of urinary incontinence (UI) following radical prostatectomy (RP). Mechanical nerve stimulation through vibration at the perineum has previously been used in the treatment of UI in women and the mechanism of action is thought to be pudendal nerve stimulation.

Subjects/patients and methods: Patients with UI after RP were included in a 12-week randomized trial between July 2012 and June 2013 at a large urological department. Initially, 39 men were included. Eight were subsequently excluded, two of these due to pain on PVS. A 24-hour pad test and a 72 hour voiding diary were collected at baseline. Participants were randomized to immediate treatment (group 1) or delayed treatment (group 2). Group 1 received PVS by daily stimulation of the glans penis with the FERTI CARE® vibrator for the first 6 weeks. Group 2 received PVS during the final 6 weeks. The primary outcome was changes in the pad test at 6 weeks. Secondary outcomes included changes in the pad test at 12 weeks and the change in number of incontinence episodes. The Wilcoxon signed rank test was used for paired analyses. Results are given as medians and ranges. The trial was registered at www.clinicaltrials.org (NCT01540656).

Results: There was a reduction of -33 g (-335 to +48 ; p=0.021) on the pad test and a reduction in daily incontinence episodes of -1 (-3.5 to +1 ; p=0.023) in group 1 at 6 weeks. There were no significant changes in group 2. At 12 weeks, group 2 had a decrease on the pad test of -8 g (-49 to

+33 ; p=0.10) and no change in incontinence episodes. A pooled analysis showed a decline on the pad test of -13.5 g (-335 to +48 ; p=0.004) before and after PVS.

Conclusion: PVS showed promise in the treatment of UI after RP. Larger trials are needed to confirm our results.

Key words

Conservative treatment; Nerve stimulation; Penile vibratory stimulation; Prostatic neoplasms; Radical prostatectomy; Urinary incontinence

Introduction

Urinary incontinence affects about 15% of patients one year after radical prostatectomy (RP) [1]. The mainstay of conservative treatment is pelvic floor exercises, however, the results are not always satisfactory [2]. The next step is often surgical treatment [3]. Therefore, non-invasive treatment options for post prostatectomy incontinence are needed.

Pudendal nerve stimulation may constitute such an option. In spinal cord injured men, stimulation of the pudendal nerve through penile vibratory stimulation (PVS) has been shown to increase the pressure in the external sphincter and the bladder capacity [4,5]. Subsequently it was demonstrated that vibratory stimulation performed on the perineum in healthy women could increase the pressure in the external urethral sphincter and improve symptoms of stress urinary incontinence [6]. Likewise, clinical experience from treating post-prostatectomy incontinence with PVS at our center has been promising (unpublished data). The purpose of the current study was to examine the effect of PVS in the treatment of male urinary incontinence following RP.

Subjects/patients and methods

The study was conducted between July 2012 and June 2013 as a 12-week prospective non-blinded randomized trial at the outpatient clinic of the department of urology, Herlev University Hospital, Denmark. Men who suffered from urinary incontinence ≥ 1 year after RP with a pad test showing a loss of at least 8 g of urine per 24 hours were eligible for the study. Patients were excluded if they had suffered from urinary incontinence prior to surgery, if they had received adjuvant radiation or hormonal therapy, if they had been treated surgically for their incontinence or if they suffered from acute illness or chronic neurological conditions.

Objective data on incontinence included a 24-hour pad test and a 72 hour voiding diary in accordance with the standards in the European Association of Urology guidelines [7]. Subjective assessment consisted of the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) [8] and the International Prostate Symptom Score (IPSS) [9]. All tests and questionnaires were completed by the participants prior to inclusion. Participants were randomized to two groups in a 1:1 ratio based on a computer generated list. The allocation sequence was implemented through numbered opaque envelopes, and the sequence was concealed until randomization. Group 1 (the immediate treatment group) was scheduled to receive PVS for the first 6 weeks while group 2 (the delayed treatment group) would serve as controls. Group 2 then received PVS treatment during the final 6 weeks of the study while group 1 was observed. No lifestyle advice regarding urinary function was given during the study and participants were instructed not to change habits for the 12 week duration of the trial. The FERTI CARE® vibrator (Multicept A/S, Frederiksberg, Denmark) was used in the study (figure 1). Patients were instructed in stimulating the ventral surface of the glans once daily with a sequence consisting of 10 seconds of stimulation followed by a 10 second pause repeated 10 times (for a total of 100 seconds of stimulation every day). The patients were then given a PVS device to use in their homes. Participants were followed up at 6 and 12 weeks with a pad test, a voiding diary and questionnaires corresponding to the baseline evaluation. In addition patients were given a global satisfaction questionnaire after PVS treatment.

The primary outcome measure was the change in leakage from baseline on the 24-hour pad at 6 weeks in the two groups. Secondary outcome measures included changes in the 24-hour pad test at 12 weeks and the change in number of incontinence episodes. Additional secondary outcomes were the changes in IPSS and ICIQ-SF and global satisfaction. Finally, pooled analyses of outcomes in

the two groups were performed. Non-parametric statistics were performed for all outcome measures with the SAS version 9.2 statistical software package for windows (Institute Inc., Cary, NC, USA). The Mann-Whitney U test and the chi squared test were used for non-paired analyses and the Wilcoxon signed rank test was used for paired analyses. All values are reported as medians and range. As the study is the first attempt to evaluate PVS in the post prostatectomy setting we were unable to conduct a formal power analysis.

Participants provided written, informed consent and the study was approved by the Danish ethical counsel and the Danish Data Protection Agency. It was registered at www.clinicaltrials.org (NCT01540656).

Results

Potential participants were identified through a review of the hospital quality assurance database and one patient was referred from a neighboring center. Thirty-nine patients were randomized. Thirty-one patients completed the first 6 weeks of the study (15 in group 1 and 16 in group 2). One patient in group 2 decided to withdraw at this time, meaning that 30 patients completed the entire 12 weeks. The flow of participants is shown in Fig. 2.

Baseline characteristics

All study participants completed pad tests, questionnaires and voiding diaries. According to the ICIQ-SF questionnaires, all patients lost urine on physical strain indication stress urinary incontinence. Twenty-three patients (12 in group 1 and 11 in group 2) reported exact numbers of incontinence episodes. The remaining eight patients reported to leak urine frequently but without noticing each incident. Neither patient characteristics nor incontinence symptoms differed between

groups at baseline (table 1). No patients had signs of biochemical recurrence at the time of inclusion and there were no significant differences in tumor characteristics between groups (data not shown). There were no statistically significant differences between the eight excluded patients and the 31 included patients except that only 1/8 of the excluded patients had undergone nerve sparing surgery compared to 17/31 of the included patients (p= 0.05).

Outcomes after PVS

There was a median reduction of -33 g (-335 to +48 ; p=0.021) in the pad test in group 1 at 6 weeks. In group 2 there was a non-significant reduction at 6 weeks of -4 g (-183 to +89 ; p=0.36). At 12 weeks the improvement in group 1 remained significant compared to baseline (-28 g ; range -163 to +31 ; p=0.04). In the delayed PVS group there was a trend toward an improvement on the pad test between 6 weeks and 12 weeks with a median of -8 g (-49 to +33 ; p=0.10). Overall, 12/15 (80%) patients had reductions on the diaper test in group 1 between baseline and 6 weeks and for eight of these patients the improvement was maintained at 12 weeks. In group 2, 11/15 (73%) patients had reductions in urinary loss between 6 and 12 weeks.

There was a significant median reduction in daily incontinence episodes in group 1 of -1 (-3.5 to +1 ; p=0.023) at 6 weeks. In group 2 there was a non-significant median increase of 0.4 (-3.7 to +3 ; p=0.54) episodes per day at 6 weeks. At 12 weeks the decrease in incontinence episodes remained significant compared to baseline in group 1 with a median change of -1 episode (-3.3 to +0.4 ; p=0.008). There was no significant change between 6 and 12 weeks in group 2 with a median change of -0.3 episodes (-2 to +4 ; p= 0.71).

Pooled analyses of both groups showed an overall median decline on the 24 hour pad test of -13.5 g (-335 to +48 ; p=0.004) and a trend toward a decrease in median daily incontinence episodes of -0.7 (-3.5 to +4 ; p=0.07) between visits before and after PVS.

To explore a possible role of pudendal nerve integrity in PVS effect (see discussion) a post hoc analysis in which patients were divided into two groups based on tumor characteristics was performed. The groups were created based on the department's standards for performing broad resection of the prostate, meaning that patients with D'Amico risk classification 1 and 3 were allocated to a narrow resection group and a broad resection group respectively. Patients with D'Amico risk classification 2 were allocated to the narrow group if they had a Gleason score of 7 (3+4) and to the broad resection group if they had a Gleason score of 7 (4+3). The Wilcoxon signed rank test showed that there was a significant reduction in the 24-hour pad test in the narrow resection group (n=17) after PVS of -28 g (-335 to +33 ; p=0.0027). Meanwhile there was no significant reduction in the broad resection group (n=13) with a median reduction of -11 g (-35 to +48 ; p=0.35).

Non-significant decreases in the ICIQ-SF scores were seen in both groups immediately after PVS while no changes were seen after observation (table 2). Meanwhile, non-significant decreases in IPSS were seen in both groups at week 6 with no subsequent changes at week 12 (table 3). In a pooled analysis of both groups the improvement in ICIQ-SF score reached statistical significance at -1 (-7 to +8 ; p=0.04) between visits before and after PVS.

Eighteen patients reported to be either very satisfied or partly satisfied (58.1%), 10 patients reported to be neither satisfied nor dissatisfied (32.3%) and 2 patients reported to be either partly dissatisfied or very dissatisfied (6.5%) with the PVS treatment. One patient did not answer the question. Twenty-four patients would recommend PVS to others (77%). Five would not recommend it and two did not answer the question.

Six out of the 39 randomized patients (15%) experienced side effects to PVS. Three patients experienced a few instances of light pain, which did not prevent them from continuing PVS within the same session. One patient experienced mild bleeding from the glans, which resolved within one day, after which PVS was reinitiated. Two patients experienced pain on stimulation, which caused them to withdraw from the study. In both cases the pain subsided after PVS was discontinued.
Five patients spontaneously reported an improvement in erectile capacity after PVS treatment (four of which had undergone nerve sparing surgery) and one patient reported to have felt orgasms for the first time since his surgery, which took place 645 days before inclusion in the study.

Discussion

Our study group recently conducted a study investigating PVS in the immediate post-operative period after RP, which showed a potential effect on erectile function but no effect on urinary continence (unpublished observations). To the authors' knowledge, this is the first study to attempt mechanical nerve stimulation in the treatment of long term post prostatectomy incontinence. PVS is non-invasive and can be performed by patients in their own home. Side effects in the current study were limited and resolved spontaneously. In conjunction with the high global satisfaction, this implies that PVS is acceptable to most patients.
The neuroanatomical background for PVS in the treatment of incontinence is thought to be pudendal nerve stimulation. Afferent nerve fibers run from the glans penis through the dorsal penile nerve to join with fibers from the pudendal nerve, which is responsible for contraction of the pelvic floor muscles and the external urinary sphincter [10,11]. Afferent nerve fibers also course from the penis to the sympathetic center in the thoracolumbar part of the spinal cord where they can affect contraction of the detrusor muscle in the bladder [12-14].

Our study showed improvements on both the 24-hour pad test and in the number of daily incontinence episodes in the immediate treatment group. Although some patients experienced a relapse after an additional 6 weeks without treatment, the overall improvements remained significant. The results with PVS in the delayed treatment group were less convincing. However, there was a numerical and borderline-significant improvement on the 24-hour pad test in the group and 73% of patients in experienced a reduction of urinary loss. In addition there was a significant reduction in the overall 24-hour urine loss after PVS when data from the two groups were pooled. This indicates that the lack of a significant change in urinary loss in group 2 is likely to be caused by the limited size of the study population.

Regarding subjective symptoms, our study showed non-significant but consistent improvements in ICIQ-SF scores with PVS in both groups, and a small but statistically significant overall improvement. Meanwhile the IPSS showed non-significant improvement throughout the study. These limited improvements are likely to reflect that while PVS improved symptoms of urinary incontinence, it rarely resulted in a complete cure. In this regard, the results of our study do not live up to what have been described with mechanical vibratory stimulation in women. A pilot study from 2007 described the results of 6 weeks of perineal stimulation in 33 stress incontinent women [6]. There were reductions in both incontinence episodes and pad use and a remarkable 73% cure rate. The differences may reflect that PVS and perineal stimulation work differently or that the effects are more pronounced in women. However, a more plausible explanation is that the pudendal nerve may have been damaged during surgery in some participants in our study. One cannot expect an effect of PVS if this is the case and it can be speculated that the method works best in patients who have not undergone a wide resection during their RP. This theory was supported by our post hoc analysis based on tumor characteristics and means that positive results may only be seen in patients with intact function of the pudendal nerve. In future trials, pudendal nerve integrity could

be tested before treatment for example by attempting to elicit the bulbocavernosus reflex. Another option is to extend the period of PVS in the hope that this will create a better response in patients with reduced function of the pudendal nerves.

The reports from some patients that PVS were of benefit to their erectile and orgasmic function are of interest as erectile dysfunction and changes in orgasmic sensation are common side effects to RP [15]. However, these factors were not evaluated systematically, and the reports should be interpreted with caution.

Due to the nature of the intervention it was not possible to blind neither the patient nor the healthcare provider. This may have been a source of bias. In addition, the use of urodynamics could have provided insight into the mechanism of action behind PVS. Another weakness of our trial is that it was not powered to perform a direct comparison between the groups. This means that, although promising, our study should serve as background for future research rather than as a basis for clinical recommendations at this time. As some patients in the immediate treatment group saw a relapse at 12 weeks, and as symptoms were reduced with PVS rather than eliminated, longer periods of PVS treatment should be attempted. In addition the effects of PVS in conjunction with lifestyle advice and pelvic floor muscle training will need specific investigation. Finally, further studies are needed to explore the potential role on PVS in restoring erectile and orgasmic function after RP.

In conclusion, PVS is a promising tool in the treatment of post-prostatectomy incontinence as the present study showed objective improvements with the treatment. In addition PVS may have effects on erectile function and orgasms. The treatment was associated with few and self-limiting side effects and PVS proved to be acceptable to most patients. Larger trials are needed to confirm our results and to find the optimal treatment protocol.

Funding and conflicts of interest

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References

1 Coelho RF, Rocco B, Patel MB et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a critical review of outcomes reported by high-volume centers. *J Endourol* 2010: **24**(12):2003-2015.

2 Campbell SE, Glazener CM, Hunter KF, Cody JD, Moore KN. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev* 2012: **1**:CD001843.

3 Lucas MG, Bosch RJ, Burkhard FC et al. EAU guidelines on surgical treatment of urinary incontinence. *Eur Urol* 2012: **62**(6):1118-1129.

4 Sonksen J, Ohl DA, Wedemeyer G. Sphincteric events during penile vibratory ejaculation and electroejaculation in men with spinal cord injuries. *J Urol* 2001: **165**(2):426-429.

5 Laessoe L, Sonksen J, Bagi P et al. Effects of ejaculation by penile vibratory stimulation on bladder capacity in men with spinal cord lesions. *J Urol* 2003: **169**(6):2216-2219.

6 Sonksen J, Ohl DA, Bonde B, Laessoe L, McGuire EJ. Transcutaneous mechanical nerve stimulation using perineal vibration: a novel method for the treatment of female stress urinary incontinence. *J Urol* 2007: **178**(5):2025-2028.

7 Lucas MG, Bosch RJ, Burkhard FC et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. *Eur Urol* 2012: **62**(6):1130-1142.

8 Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn* 2004: **23**(4):322-330.

9 Barry MJ, Fowler FJ, Jr., O'Leary MP et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992: **148**(5):1549-1557.

10 Shafik A, el-Sherif M, Youssef A, Olfat ES. Surgical anatomy of the pudendal nerve and its clinical implications. *Clin Anat* 1995: **8**(2):110-115.

11 Schraffordt SE, Tjandra JJ, Eizenberg N, Dwyer PL. Anatomy of the pudendal nerve and its terminal branches: a cadaver study. *ANZ J Surg* 2004: **74**(1-2):23-26.

12 Reitz A, Schmid DM, Curt A, Knapp PA, Schurch B. Afferent fibers of the pudendal nerve modulate sympathetic neurons controlling the bladder neck. *Neurourol Urodyn* 2003: **22**(6):597-601.

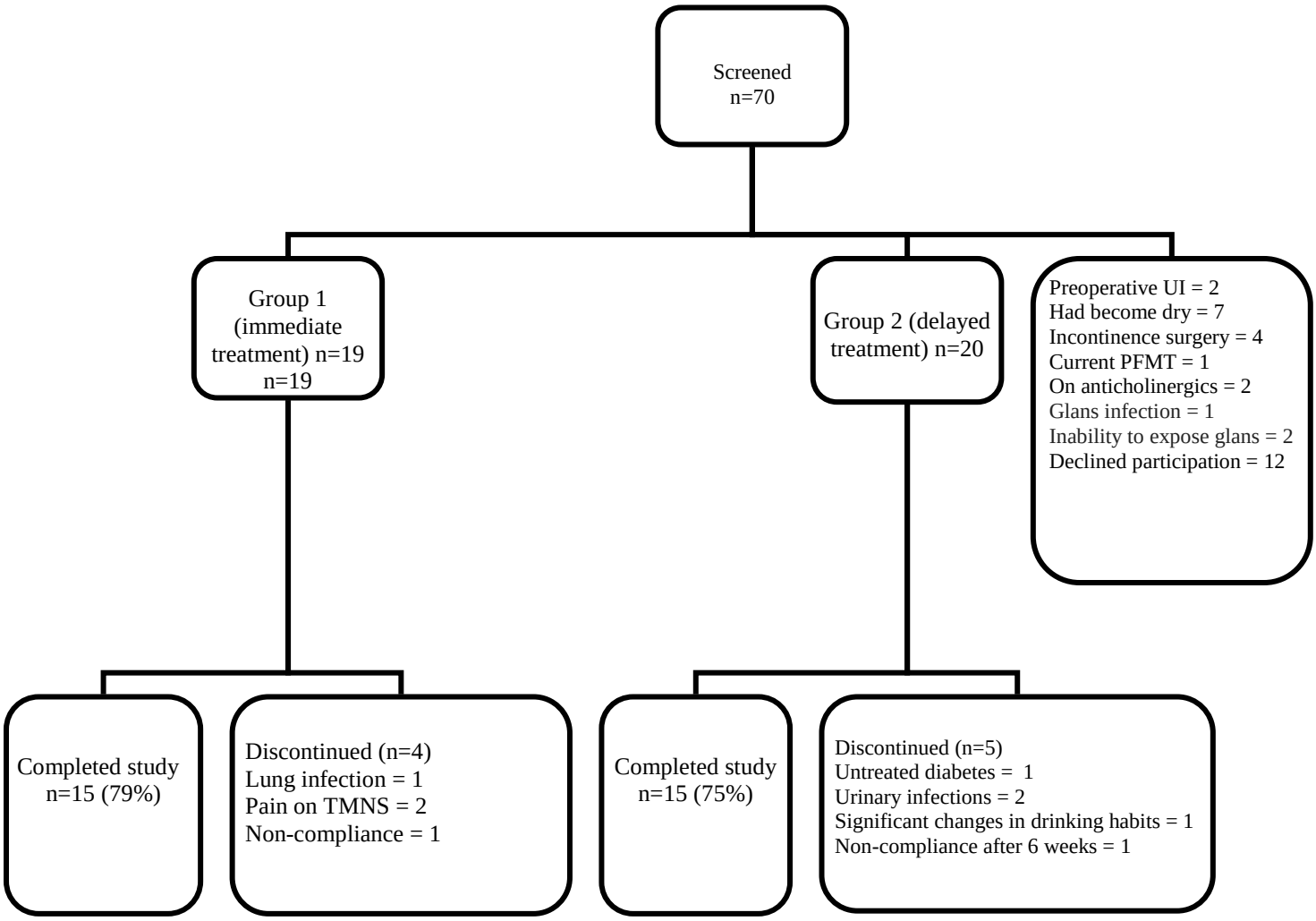
13 Laessoe L, Sonksen J, Bagi P et al. Effects of ejaculation by penile vibratory stimulation on bladder reflex activity in a spinal cord injured man. *J Urol* 2001: **166**(2):627.

14 Farag FF, Martens FM, Rijkhoff NJ, Heesakkers JP. Dorsal genital nerve stimulation in patients with detrusor overactivity: a systematic review. *Curr Urol Rep* 2012: **13**(5):385-388.

15 Benson CR, Serefoglu EC, Hellstrom WJ. Sexual dysfunction following radical prostatectomy. *J Androl* 2012: **33**(6):1143-1154.

Figure 1: The FERTI CARE® vibrator (Multicept A/S, Frederiksberg, Denmark). The device was set to an amplitude of 2 mm and a vibration frequency of 100 Hz. Patients were instructed in stimulating the frenulum once daily with a sequence consisting of 10 seconds of stimulation followed by a 10 second pause repeated 10 times (for a total of 100 seconds of stimulation every day).

Figure 2: The flow of patients in study



PFMT: pelvic floor muscle training

Table 1: Patient characteristics and baseline urinary symptoms

	Median age (years)	Nerve-sparing	Robot-assisted surgery	Median amount of urine loss per 24 hours (g)	Median number of incontinence episodes per 24 hours	Median IPSS	Median ICIQ-SF score	Median time since surgery (days)
Group 1	67 (61-76)	Yes: 9 No: 6	Yes: 9 No: 6	60 (13–683)	4 (0.3-14)	9 (1-18)	13 (7-21)	593 (397-1188)
Group 2	67 (51-74)	Yes: 8 No: 8	Yes: 11 No: 5	41 (8-400)	4.2 (1-13.7)	9.5 (3-25)	14 (9-20)	573.5 (393-1313)
p-value	0.73	0.58	0.61	0.65	0.42	0.61	0.75	0.95

ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form

IPSS: International Prostate Symptom Score

Table 2: Median (range) ICIQ-SF score changes throughout the study

ICIQ-SF score change	Group 1	Group 2
Baseline to week 6	- 2 (-6 to +8 ; p=0.18)	+ 0.5 (-5 to +5 ; p=0.93)
Week 6 to week 12	0 (-3 to +7 ; p=0.93)	- 1 (-7 to +2 ; p=0.23)

ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form

Table 3: Median IPSS score changes throughout the study

IPSS change	Group 1	Group 2
Baseline to week 6	- 1 (-8 to +7; p=0.49)	- 1.5 (-6 to +5 ; p=0.27)
Week 6 to week 12	0 (-7 to +4; p=0.46)	0 (-8 to +5 ; p=0.92)

IPSS: International Prostate Symptom Score