Discussion and conclusion

10

Introduction

This thesis starts with the question whether slings, old and new, for both male and female patients, can live up to the expectations of both patients and physicians by being both safe and effective in curing stress urinary incontinence (SUI). Secondly, the question is raised whether sling surgery is anatomically safe with regard to those nervous systems that are essential for the sexual function or may actually be responsible for iatrogenic neurological damage during placement.
We addressed these questions by critically evaluating the methods of introduction, the efficacy and the (anatomical) safety of various slings used for curing SUI.

Main findings

The first part of the research question was addressed by evaluating the methods of introduction and efficacy of both old and new slings (chapter 2-4). In **chapter 2** the methods of introduction of new mid-urethral slings (MUS) were assessed and it was revealed that there is a lack of pre-launch data in more than 70% of the marketed slings. In **chapter 3** we presented the clinical results of a 'new generation' sling, the MiniArc™, in a population of 77 women after 1 year. These results show that only 44% of the patients was (subjectively) cured after 1 year, suggesting that the MiniArc™ is less effective in the treatment of SUI than the TVT™.
Chapter 4 describes the results of sling surgery in a non-selected population of 255 women after a mean follow-up of 15 months. The conclusion of this study was that, although sling surgery is both effective and efficient in curing SUI, patient characteristics and confounding variables can seriously influence the outcome of surgery and should therefore always be discussed with the patient. Moreover, the results of chapter 4 confirmed the beneficial effects of simultaneous pelvic organ prolapse (POP) surgery and MUS placement as this provided significant improvements in both urinary symptoms and QoL, without any negative effects in terms of SUI related symptoms.
The thesis continues in **chapter 5** with a clinical article that discusses the beneficial effects of concomitant collagen sling placement following partial removal of a primary synthetic MUS due to late complications (erosion and/or displacement). The outcome of this study was that, although this procedure shows some promising results for specific complications in terms of continence, more research on the individual approach of late complications will be needed in the future. Despite the fact that this chapter did not aid in answering the research question as such, it does shed (some) light on the complexity and diversity of (late) complications that can arise following sling surgery.

A review of literature on the results of sling surgery in male patients suffering from urinary incontinence following a transurethral resection of the prostate (TURP) is provided in **chapter 6**, together with an evaluation of a new sling (Virtue®) in this specific group. The review shows that literature on this subject is scarce and suggests that sling surgery in this group is significantly less successful in comparison to other patient groups. The clinical trial on the Virtue® sling observed continence in 4/8 (50%) patients, with another 2 (25%) patients stating an improvement in their SUI at the 12-month postoperative follow-up. This paper concluded that the new Virtue® sling shows promising results in being an efficient and safe device for the treatment of SUI following a TURP, but larger cohorts will be needed to confirm these results.

The final 2 chapters answer the second part of the research question by describing the potential perioperative damage caused by sling surgery to the pelvic (neuro) anatomy in male and female patients. In **chapter 7** the autonomic and somatic pelvic pathways and their relationship to the TVT™ or TVT-O™ were assessed by the dissection of 14 female hemi-pelves. Moreover a three-dimensional reconstruction of the neuroanatomy of the clitoris was created by studying serially sectioned and histochemically stained pelves from 11 female fetuses. The results showed that the dorsal nerve of the clitoris (DNC) is located inferiorly to the pubic ramus and was not disturbed during the placement of the TVT-O™. However, the autonomic innervation of the vaginal wall was disrupted by the TVT™ procedure, which could lead to an altered lubrication-swelling response.

Chapter 8 starts with the description of a patient in which the AdVance™ male sling procedure resulted in the complete interruption, or neurotmesis, of the right dorsal nerve of the penis (DNP). Due to this complication, a study was conducted to further describe the anatomical relation between the AdVance™ male sling and the DNP based on the dissection of 6 adult male pelves. Results of this study showed a mean distance between the sling and DNP of 4.1 mm, whilst it was situated directly next to the DNP in 4 out of 12 (33%) hemi-pelves. The distance of the sling to the obturator neurovascular bundle was 30 mm or more in all 6 bodies. In conclusion, although damage to the DNP caused by the AdVance™ male sling procedure appears to be an extremely rare complication, the proximity of the AdVance™ to the DNP could possibly pose a risk that should be taken into consideration by physicians and patients when opting for surgery.

Implications and recommendations

The introduction of new slings

New slings are often introduced without any structured scientific pre-launch evidence on their effectiveness and safety (1;2). In April 2014, the U.S. Food and Drug Administration (FDA) issued two proposed orders for the re-classification of surgical meshes used for transvaginal pelvic organ prolapse (POP) repair. The first order would re-classify these medical devices from class II, which generally includes moderate-risk devices, to class III, which generally includes high-risk devices. The second order would require companies to provide clinical data in a premarket approval (PMA) application to support the safety and effectiveness of the device. On the fifth of January 2016 the FDA issued their final orders for the reclassification of these products and the requirement of a PMA. However, the FDA also clearly stated that these orders do not include surgical meshes indicated for the surgical treatment of SUI, meaning that these slings can still be introduced without any supporting premarket evidence (*).
We believe that in order to achieve the best and safest possible products for patients new standards should also be introduced for the marketing of slings as soon as possible. These standards should include the four obligatory points shown below, followed by a compulsory registration of the first 1,000 consecutive patients (1).

1. *Comprehensive and exact data on the physical properties of the product*
2. *Data on the biological properties of the product following implantation from high-quality animal studies*
3. *Anatomical studies on cadavers*
4. *A well-constructed and documented cohort study*

The results of the MiniArc™ in chapter 3 further illustrate the fact that a new product and technique is not necessarily equal to, or better than, a gold standard such as the TVT™ (3). The disappointing results, combined with the fact that no premarket studies had been performed on this particular sling, strengthen our belief that new standards for the introduction of new slings are indeed very much needed. In the future these new standards should be able to prevent inferior or even dangerous products from reaching the market and will ultimately result in better patient care.

* (https://www.federalregister.gov/articles/2016/01/05/2015-33163/effective-date-of-requirement-for-premarket-approval-for-surgical-mesh-for-transvaginal-pelvic-organ), http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm262301.htm

Individuality in informed consent and approach of late complications

As no two patients are equal, it can be derived that not every patient will benefit equally from the same surgical procedure. This also applies to MUS surgery and according to the EAU guideline these confounding variables could play a large role in determining the outcome of surgery (4). Current research on MUS surgery frequently tends to exclude patients with confounding variables and only present results of the 'perfect' patient group (BMI<35, no surgical history, no concomitant surgery etc.) (5-8).

In chapter 4 we showed that when a study is performed on a 'raw' and non-selected population overall results may indeed be disappointing at first sight. If however a population is large enough to perform subgroup analysis, one can then accurately describe and compare the results of the individual patient groups. Future studies on MUS surgery should therefore aim to minimize their selection bias, rather than just present the results of the 'perfect patient'. This information can and should then be used to provide more individualised informed consent and prevent overestimating the outcome of surgery (9).

When a surgical procedure is as regularly performed as sling surgery, it will inevitably lead to higher numbers of (postoperative) complications. Two of the most common late postoperative complications of sling surgery in women are erosion of the mesh material and displacement of the tape towards the bladder neck. Still, where local treatment such as cleaving the sling may be possible in some, the complete or partial removal of the mesh material is unavoidable in others. If a primary sling is (partly) removed after erosion or displacement in an incontinent patient, the concomitant placement of a second sling should theoretically enhance postoperative continence levels. In chapter 5 we observed that this was in fact not the case, as continence was achieved in less than one-third of our study population (10). The analysis of the, somewhat disappointing, results together with a review of literature showed that studies on this subject are rare and that, although some patients are seemingly suffering from a similar problem, there is no such thing as a general approach when dealing with rare complications (11-14). In conclusion we can say that when dealing with such a complex population, every specific case has to be approached as being a unique problem on itself. Moreover it becomes clear that mid-urethral slings can be responsible for a significant loss in quality of life due to late complications and more research on the individual approach of specific complications will be needed in the future to provide optimal patient care.

Sling surgery for male patients with SUI

When discussing postoperative (iatrogenic) SUI in male patients, the causes can be divided into two main groups; the first following a radical prostatectomy (RP), the second following a TURP. Complication rates following a TURP are generally low but are frequently encountered following the large number of surgical procedures. SUI

after a TURP occurs in 1.8% to 5.0% of patients (15-18). While sling surgery following a RP is becoming increasingly popular and shows respectable success rates between 40 and 91%, little is actually known about the efficacy in patients following a TURP (19;20). A literature search on this matter revealed that there are only a few studies describing a handful of TURP patients, but success rates are generally lower than in patients following a RP (21-25). The results of the small case series in chapter 6 showed that, in contrast to other slings in current literature, the Virtue® male sling appears to be as effective in post-TURP patients as in patients with a RP in their medical history. To review these preliminary findings from a scientific perspective, knowledge on the actual pathophysiology of iatrogenic SUI is paramount. Whereas SUI following a RP may be caused by either sphincter dysfunction or bladder dysfunction, SUI following a TURP is usually caused by damage to the proximal part of the (rhabdo) sphincter distal to the seminal colliculus or verumontanum (26). The dual design of the Virtue® male sling that combines both perineal urethral compression and proximal urethral relocation, support our hypothesis that this sling is better suited for post-TURP SUI than other conventional male slings that work through either compression or relocation of the urethra (27-31).

When looking at the results of sling surgery for male SUI, one has to take into consideration that the surgical gold standard, in this predominantly older patient group, still is the complication prone AUS (artificial urethral sphincter). So, understandably, the relatively minimally invasive male slings have gained popularity in the treatment of SUI over the last two decades. Nevertheless it remains the question whether sling surgery is indeed the treatment of the future for the specific group described in this thesis and more research on the subject will be needed.

Sling surgery and sexual function

Vaginal sling procedures may have a negative effect on sexual function through neurovascular damage to the genital structures. To discern between the possible negative effects due to neurovascular damage in combination with the positive side-effects on sexual functioning of the surgical procedure itself (regaining continence), is virtually impossible. By describing the anatomical relationship between the somatic and autonomic pathways of the clitoris and the TVT™/TVT-O™ in chapter 7 of this thesis, more light was shed on this intricate question. The proximity of the autonomic nerves of the clitoris and the TVT™, means that this procedure will almost certainly cause neurological damage that may result in disturbances in the swelling and lubrication response during arousal. These findings are retrospectively confirmed by a study by Caruso et al. in 2007, which showed a significant decrease in the clitoral blood flow after a TVT™ procedure (32). Furthermore the proximity of the DNC and the TVT-O™ shows that, although rare, neurological damage could occur during surgery (33).

In the future these possible negative side-effects on sexual function should be a standard part of the informed consent provided when opting for surgery and could eventually lead to different groups of patients selecting different slings as a result of this information.

In chapter 8 this thesis continues with a paper that further clarifies the (neuro-) anatomical relationship between the AdVance™ male sling and the DNP. Based on basic anatomical knowledge, it can be estimated that the anatomical route of a male transobturator sling, such as the AdVance™, is close to certain important urogenital nerves such as the DNP. When consulting the literature on this subject it is safe to say that the complication encountered in our clinic (neurotmesis of the DNP) is indeed very rare, but any substantial anatomical research since the introduction of this sling, other than the study in this thesis, is lacking.

In an editorial comment on this chapter, the author questions the methodology and validity of the clinical implications based on the conclusions of this paper. In our conclusion we state that the proximity of the AdVance™ to the DNP could potentially pose a risk that should be taken into consideration by physicians and patients when opting for surgery. Nonetheless, by claiming that there is no proven clinical risk and numbers in our study are lacking, the need to inform patients of this potential risk is dismissed. In contrast, the study itself is commended (34). In another response to our paper by the inventor of the AdVance™ in an expert's summary, the author first points out certain limitations in the methodology of this study and then emphasizes the fact that in his clinical experience, the complication of neurotmesis of the DNP has never been encountered (35).

From the reactions on both chapter 7 and 8 there are several lessons to be learned. Firstly it is nearly impossible to extrapolate the findings of a relatively small in mortuo study directly into a clinical setting without substantial 'in vivo' functional evidence to back up the findings. Secondly, when conducting basic in mortuo anatomical research on this scale, the lack in numbers and the (obvious) difference between cadaveric and live tissue will always remain a valid argument to challenge the substance of such a study.

This leaves us with the next dilemma; is it enough for a small(er) study to act as a thought provoking contribution to our knowledge, or should it have clinical consequences as well? As of present, a (central) registry to track the outcomes and adverse events of (new) slings does not exist and basic anatomical research on this subject remains rare. The lack of such a registry will always make it difficult to put the findings of smaller observational studies into perspective and make clinical recommendations. In the end, whether a surgeon chooses to merely acknowledge the information, or actually uses it to inform his or her patients, remains up to them. Nevertheless, taking the tens of thousands of slings being implanted around the world each year into consideration,

it is obvious that more research should be conducted to investigate these potential surgical complications.

Future perspectives and conclusion

Will sling surgery remain the treatment of choice in the endless battle against SUI? Can newer techniques make sling surgery even less invasive (and safer) without compromising the success rate? Will new standards to monitor the introduction and marketing of new slings be introduced in the near future? Or will sling surgery be replaced altogether by a new treatment that focuses on urethral function rather than urethral support?
These are all questions that remain unanswered up to present. It is clear however that these last decades (synthetic) slings have made a huge, and largely positive, impact on the treatment of urinary incontinence. Nevertheless, the medical community should always strive to provide the best and safest care possible for its patients, meaning one has to assure him- or herself on the safety and efficacy of a new medical device before using it in practice. In this thesis we conclude that many slings were, or still are, freely available on the market without any proper pre-market research. By conducting structured studies adhering to predetermined protocols, that include both in vivo as well as ex vivo elements, prior to the introduction of a new sling, combined with the introduction of a central registry to track the outcomes and adverse events of new slings, a safer patient environment can and should be created in the future.

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