Urethral function in overactive bladder syndrome

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CHAPTER 7

SUMMARY (ABSTRACTS)

CHAPTER 2

Introduction:

Past research has demonstrated that the urethral tonus is mainly under sympathetic control. Since five years, a beta 3 adrenoceptor (ADRB3) agonist is available in treatment of overactive bladder syndrome. The presence of ADRB3 within the human urethra has not been demonstrated to date. Presence of ADRB3 in the urethra could influence urethral tonus. The aim of this study is to investigate the presence of ADRB3 in the human female urethra.

Material and Methods:

We performed anatomical studies in 5 female specimen. Three specimen were obtained from the body donation program, two from female patients with muscle invasive bladder cancer, where radical resection of bladder and urethra was performed. The urethra up till the bladder neck was separated from the rest of the bladder and freshly obtained for this study. For demonstrating ADRB3 expression, we used rabbit polyclonal anti-human ADRB3 LS-A4198 .

Results:

Expression of ADBR3 was demonstrated in the epithelial layer of all urethral parts, except at the level of the meatus. The level of ADRB3-expression was highest in the mid-urethra. There was no direct contact between ADRB3 and nerve tissue. ADRB3 expression was also demonstrated in the stratified muscle layer at the level of external urethral sphincter.

Conclusions:

This is the first study to demonstrate expression of ADRB3 in the human female urethra. There is absence of a direct connection between ADRB3 and nerve tissue.

CHAPTER 3

Introduction:

The clinical relevance of urethral pressure variations (UPV) in the pathophysiology of over active bladder syndrome (OAB) has remained controversial to date. Some studies report an association with OAB and/or detrusor over activity (DO). Recently the International Consultation on Incontinence – Research Society recommended new clinical research to be performed on this subject. We provide a systematic review of the literature to specify this recommendation.

Methods:

Literature search was performed in PubMed, Embase, Web of Science, Cochrane, Central, Cinahl, Academic Science Premier, ScienceDirect and WileyOnline using a sensitive search string combination. All authors independently reviewed and scored full text papers and consensus about methodological quality was obtained according to Oxford Level of Evidence (LoE).

Results:

487 abstracts were screened, 25 papers met all predefined inclusion selection criteria. Incidence figures of UPV varied between 2 and 95%. Studies are of poor methodological quality with Oxford LoE scores of 3B and 4. Measurement methods and techniques show a large variety. The abovementioned association of DO/OAB with UPV is however rather consistently reported.

Conclusions:

UPV, and detrusor (over-) activity, may exist as separate entities, may coincide or may be pathophysiologically associated and may or may not be a cause of OAB syndrome. A large variation in measurement techniques for UPV in a variety of patient populations is reported, which hinders fundamental research as well as clinical progress. Clinical relevance of UPV and consequences for treatment therefore are yet to be established. Future prospective research with well-defined patient population and standardised urodynamic measurement techniques is needed. Results of standardized and objective evaluations should be compared to clinical signs and symptoms by validated questionnaires to be able to offer personalised management for OAB patients.

CHAPTER 4

Introduction:

During filling cystometry, urethral pressure variations (UPV) can be observed. The clinical relevance and a clear definition of this phenomenon are still matter of debate. For further research and definition of UPV, it is important to determine how this condition can best be demonstrated. The purpose of this study is to compare continuous urethral pressure measurements with a single urethral sensor catheter and a triple urethral sensor catheter in demonstrating UPV.

Methods:

75 adult female patients requiring urodynamic investigation enrolled in this prospective study. All patients underwent two series of filling and voiding cystometry. One series was performed with a dual air-balloon sensor urodynamic catheter, the other series with a triple urethral sensor catheter. Urethral pressure variations (UPV) were defined as urethral pressure drop exceeding 30 cmH2O.

Results:

The prevalence of UPV was 37.3% (28 out of 75 patients), more common than detrusor overactivity. The triple urethral sensor catheter was more sensitive than the single urethral sensor catheter: In 8 patients UPV was demonstrated with both catheters and in 18 patients only in the measurement with the triple urethral sensor catheter. This difference in detection was significant ($p<0,001$).

Conclusion:

There is additional value in measurement with triple urethral sensor catheter for demonstration of UPV during filling cystometry. Currently, continuous measurement of urethral pressure during filling cystometry and UPV are not defined within ICS terminology. The single urethral sensor catheter is useful for a start, however it demonstrates less than half of all UPV

CHAPTER 5

Introduction:

Urethral instability (URI) has in the past been defined by the International Continence Society (ICS) but was excluded of ICS terminology and definitions shortly after because of lack of consensus about the clinical importance of this phenomenon. Recently, interest for URI and its possible role in overactive bladder (OAB) increased again. In the last decade, a beta 3 adrenoreceptor agonist (mirabegron) is approved for treatment of OAB. The effect of mirabegron on urethral pressure during filling cystometry is unknown. The aim of this study was to assess the influence of mirabegron on urethral pressure variations during urodynamic investigation and the association of symptoms and voiding diary data before and on treatment.

Methods:

This prospective study included 51 consecutive adult female patients, referred with OAB. Patients were evaluated with a voiding diary, two validated questionnaires and two urodynamic investigations, one before and one after six weeks of treatment with mirabegron. URI was defined as an urethral pressure drop exceeding 30 cmH2O during filling cystometry.

Results:

The prevalence of URI was 31% at initial urodynamic investigation, and 19% at second investigation. URI is more common than DO with 18% prevalence at initial evaluation. Treatment with mirabegron resulted in significant changes in symptoms and urodynamic sensory markers in patients with URI.

Conclusion:

Urethral pressure variations are significantly reduced by treatment with mirabegron in patients with URI. URI seems to have a predictive value in treatment choices for OAB. Future research should elucidate this.

CHAPTER 6

Introduction:

We present the results of a pilot study performed in 5 female patients with overactive bladder symptoms (OAB), combined with urethral instability (URI), treated with subtrigonal Botulinum toxin-A (BoNT-A) injections. Treatment modalities for OAB have in common that they interfere in any part of efferent and afferent signaling from the bladder to the brain, the difference is in the localization and extent of interference. We hypothesized that patients with OAB symptoms and URI could benefit more from a treatment with the mode of action at the urodynamically identified problem.

Methods:

This a retrospective description of the pilot study we performed. Four patients had a long history of refractory idiopathic OAB symptoms, in one patient the main complaint was painfull bladder syndrome. In all patients URI was demonstrated during filling cystometry. Treatment was started with subtrigonal injections of 10cc lidocaine 1%. If OAB symtoms improved with more than 50%, treatment continued with subtrigonal injections with BoNT-A.

Results:

Four out of 5 patients OAB symptoms improved more than 50% after subtrigonal BoNT-A injections. URI disappeared in one patient after treatment. In three other patients, the maximum amplitude of the urethral pressure variations decreased from more than 40cm H2O up to a maximum of 20 cm H2O. The most remarkable change was the improvement in first sensation of filling.

Conclusions:

Chemical denervation by subtrigonal BoNT-A injections in patients with OAB combined with URI, resulted in improvement of refractory OAB symptoms in all patients with refractory OAB as their main complaint in this study.