



INTERNATIONAL CONTINENCE SOCIETY EDUCATIONAL COURSE

JANUARY 26 - 27, 2007
ABU DHABI, UNITED ARAB EMIRATES



PROGRAMME

ICS PARTNERS:   **Medtronic**

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CONTENTS

Greetings	4
Sponsors & Exhibitors	5
ICS History and Committees	6
Meet the Speakers	7
General Information	8
Programme	9
Course Material	13



INTERNATIONAL CONTINENCE SOCIETY EDUCATIONAL COURSE

GREETINGS

Welcome to Abu Dhabi!

In extending the scientific role of the International Continence Society all over the world, welcome to Abu Dhabi the largest of the United Arab Emirates.

For 35 years the ICS has held an internationally recognised multi-disciplinary annual meeting of the highest scientific quality and in recent years there have been pre-meeting workshops and ICS educational courses. Now the ICS Education Committee have created the stand-alone ICS educational course outside of the annual meeting with the aims of discussion and exchanging experiences with colleagues of different countries.

These non-profit making courses are intended to appeal to younger doctors, nurses, physiotherapists and scientists who may find it difficult and too expensive to attend the annual ICS meeting but are keen to understand the important aspects of the ICS and to interact with other ICS members and listen and learn from relevant topics.

We have designed this course to bring together international speakers of different disciplines to share their experiences with all the delegates adding to the value and effectiveness of the event. There are many topics that are being covered by the course and we hope that you will receive an overview of incontinence issues.

Besides the course enjoy what the Emirates have to offer. Everything in Abu Dhabi is modern, sleek and shiny. Join us on Friday evening at the welcome reception and mingle with colleagues, speakers and the exhibitors with a cocktail and food. Then why not take a stroll down the Corniche or enjoy the duty free shopping at the various shopping malls.

We hope that the Educational Course fulfils your expectations and in return all we ask is that you complete your evaluation form so that we learn from our experiences to make better Educational Courses in the future.

A blue ink signature of Linda Cardozo, consisting of a stylized 'L' and 'C' followed by a horizontal line.

Linda Cardozo
Education Committee Chairperson

A blue ink signature of Sherif Mourad, written in a cursive style.

Sherif Mourad
Course Coordinator



SPONSORS and EXHIBITORS

Sponsors



Exhibitors

BK - Medical

Laborie Medical Techs N.V.

Gynecare Johnson & Johnson



INTERNATIONAL CONTINENCE SOCIETY EDUCATIONAL COURSE

ICS HISTORY AND COMMITTEES

Visit our website: www.icsoffice.org

The International Continence Society was founded in 1971 by Eric Glen under the name of the “Continent Club” and held its first annual meeting the same year in Exeter where 60 participants attended. In 2005, we have over 2,000 members from 70 different countries with over 3,000 delegates attending ICS 2004 in Paris.

The ICS aims to provide education and advancement of sciences concerned with urinary tract and pelvic dysfunction including urology, neurourology, gynaecology and urodynamics. The Society also promotes research into the causes, remedies and relief of incontinence and provides access to the results of that research via website, email, post, telephone, paper publication, newsletters and presentations, annual congresses and courses.

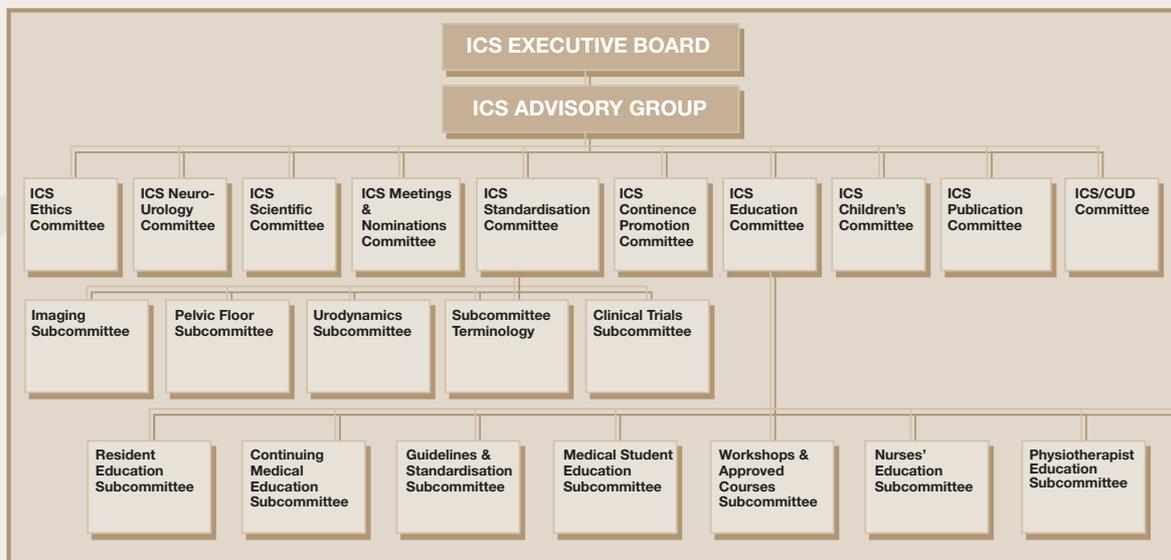
Our Annual Meeting is hosted by a different member each year, selected by members ballot four years in advance.

- 2005 Montreal, Canada
Chair, **Jacques Corcos**
- 2007 Rotterdam, The Netherlands
Chair, **Ruud Bosch**
- 2009 San Francisco, USA
Chair, **Ted Arnold**
- 2006 Christchurch, New Zealand
Chair, **Ted Arnold**
- 2008 Cairo, Egypt
Chair, **Sherif Mourad**

Our membership subscription remains at £50 per annum and includes:

- Six bi-monthly copies of the Journal Neurourology and Urodynamics
- 40% reduction in registration to our Annual Meeting
- The ICS members’ book and certificate
- Two bi-annual ICS newsletters
- Access to other members worldwide
- Information and education via our website, office, courses and meetings.

Today, the society employs four fulltime staff at its head office in Bristol, UK and has an Executive Board comprising four voluntary directors. There is also an Advisory Group and many committees dedicated to various tasks ensuring the Society’s charitable objectives are maintained (see chart below).



ICS Education Committee

Prof. Linda Cardozo (Chairperson)
 Prof. Walter Artibani
 Prof. Carlos Levi D'Ancona
 Dr. Roger Roman Dmochowski
 Dr. Michael Halaska
 Mr. Hashim Hashim

Dr. John P.F.A. Heesakkers
 Dr. Vikram Khullar
 Prof. Helmut Madersbacher
 Dr. Menahem Neuman
 Prof. Flavio Trigo Rocha
 Dr. Peter K. Sand

Dr. Ajay Singla
 Mrs. Marijke C. Ph.Slieker ten Hove
 Mrs. Amanda Wells
 Prof. Jean-Jacques Wyndaele



MEET THE SPEAKERS

(List in alphabetical order)



Ayman Al Qatawneh



Waleed Al Taweel



Walter Artibani



Linda Cardozo



Marcus Drake



Hashim Hashim



Helmut Madersbacher



Sherif Mourad



Ismail Osman



Diaa Rizk



Stefano Salvatore



Hassan Shaker



Marijke Slieker-ten Hove



Tony Smith



Mandy Wells



Jean Jacques Wyndaele



INTERNATIONAL CONTINENCE SOCIETY EDUCATIONAL COURSE



GENERAL INFORMATION

Course Venue

Millenium Hotel Abu Dhabi
P.O. Box 44486
Abu Dhabi
U.A.E
Tel: +971 (0) 2 626 2700
Fax: +971 (0) 2 626 033

Language

Lectures and presentations will be given in English.

Clothing

Casual for all occasions.

Registration and Information Desk

The Registration and Information Desk will operate at the following times:

Friday January 26, 2007	10:00 – 18:00
Saturday, January 27, 2007	08:00 – 17:00

Welcome Reception

At the end of sessions on Friday, January 26, 2007

CME Accreditation

EU-ACME – This Educational Course is accredited within the EU-ACME programme by the European Board of Urology Accreditation Committee with 8 credits. These credits are stated on your certificate of attendance. In order to receive your certificate of attendance please complete your evaluation form and hand in at the registration desk. If you are a member of the EU-ACME programme then please present your membership card for scanning at the registration desk to automatically receive your credits.



International Continence
Society Educational Course



PROGRAMME



INTERNATIONAL CONTINENCE SOCIETY EDUCATIONAL COURSE

PROGRAMME

FRIDAY, JANUARY 26, 2007

10:00 – 13:30	Registration
13:30	Lunch
14:30	Welcome Sherif Mourad Aims and objectives of course Linda Cardozo
14:45	ICS Mission & Education Committee Walter Artibani
15:00	ICS Terminology Linda Cardozo
15:30	Good Urodynamic Practice Part 1 Coordinator: Sherif Mourad Hashim Hashim Marcus Drake
16:00	Coffee Break
16:20	Good Urodynamic Practice Part 2 Coordinator: Sherif Mourad Hashim Hashim Marcus Drake
16:40	ICI Algorithms Coordinator: Linda Cardozo 16:40 Men Walter Artibani 16:50 Women Linda Cardozo 17:00 Elderly Helmut Madesbacher 17:10 Neurogenic Jean-Jacques Wyndaele 17:20 Discussion
17:30	How to deal with mixed incontinence Stefano Salvatore
17:55	Discussion
18:00	Close & Welcome Reception



SATURDAY, JANUARY 27, 2007

09:00	The emerging role of the Continence Specialist Nurse Mandy Wells
	09:25 Discussion
09:30	Assessment of the pelvic floor musculature Marijke Slieker-ten Hove
	09:55 Discussion
10:00	Ageing of the pelvic floor Diaa Rizk
	10:25 Discussion
10:30	Coffee Break
11:00	“My drug is best for OAB” Coordinator: Walter Artibani
	11:00 Tolterodine (Pfizer) Tony Smith
	11:10 Oxybutynin (Janssen Cilag & Aspen) Hassan Shaker
	11:20 Darifenacin (Novartis) Stefano Salvatore
	11:30 Solifenacin – Vesicare (Astellas) Hashim Hashim
	11:40 Propiverine (Apogepha) Helmut Madersbacher
	11:50 Oxybutynin patch (UCB Pharma) Linda Cardozo
	12:00 Discussion
12:15	Neurourology Update Coordinator: Jean-Jacques Wyndaele Helmut Madersbacher
	12:50 Discussion
13:00	Lunch



INTERNATIONAL CONTINENCE SOCIETY EDUCATIONAL COURSE

SATURDAY, JANUARY 27, 2007 (Cont.)

- 14:00 **Debate: Should Urodynamics be carried out prior to all surgery for SUI?**
Coordinator: **Sherif Mourad**
- 14:00 For
Tony Smith
- 14:10 Against
Marcus Drake
- 14:25 Discussion
- 14:30 **Injection Therapy**
Coordinator: **Sherif Mourad**
- 14:30 Bulking Agents in ISD
Sherif Mourad
- 15:00 Botox in LUT
Ismail Osman
- 15:25 Discussion
-
- 15:30 Coffee Break
-
- 16:00 Diagnosis and management of incontinence in men
Coordinator: **Walter Artibani**
Jean-Jacques Wyndaele
- 16:25 Discussion
- 16:30 "My tape is best for SUI"
Coordinator: **Linda Cardozo**
- 16:30 TVT – TVT O – TVT Secure (Gynecare)
Ayman Al Qataweh
- 16:40 SPARC – MONARC (AMS)
Hashim Hashim
- 16:50 Aris (Coloplast)
Hassan Shaker
- 17:00 Uretex (Bard)
Waleed Al Taweel
- 17:10 Discussion
- 17:20 Closing Words
Sherif Mourad
- 17:30 Close



International Continence
Society Educational Course



COURSE MATERIAL

ICI ALGORITHMS: Neurogenic

Jean-Jacques Wyndaele

The innervation of the lower urinary tract (LUT) is both complicated and subtle. The system works in an interrelated action of autonomic and somatic nerves, with both afferent and efferent branches and under mostly indirect voluntary control which in itself is subject to several influences and regulating mechanisms. It does not surprise that LUT function gets disturbed in most of the neurologic pathologies and such with different prevalence and extent.

The diagnosis of neurologic bladder comes from information gathered by clinical assessment including history, with symptoms and signs, physical examination with neurological tests, urine evaluation. However these do not permit a detailed individual diagnosis. Urodynamic investigation and preferably videourodynamic testing is strongly advocated. Evaluating sensation will add to the diagnosis. A combination of all tests offers the possibility of typing the neurologic dysfunction with specification of detrusor, bladder neck and striated sphincter activity and the relation between these. Important is the measuring of the intravesical pressure development during filling and voiding as one of the main goals of treatment will be to have a low pressure urine reservoir, continence and appropriate regular emptying to avoid upper urinary tract complications and urinary infection. The individual diagnosis will permit the choice of the most appropriate treatment.

Conservative treatment can consist of behavioural therapy, catheterisation, intake of drugs, electro stimulation. Triggered voiding is to be used only in patients whose situation has proven to be urodynamically safe and stable and who can manage reflex incontinence. Bladder expression is basically dangerous and its indications are limited. Timed voiding, habit retraining, prompted voiding can be part of each individual rehabilitation. Clean intermittent catheterisation is safe and effective in the short-term and in the long-term and CIC is recommended as first choice of treatment for those with inability to empty the bladder adequately and safely, but proper education and teaching is necessary. Indwelling catheters transurethral /suprapubically are no safe methods for long-term use. If indicated strict care can prevent some of the complications. External appliances can be needed for controlling urinary incontinence in neurologic patients. Bladder relaxing drugs are used frequently to create a low pressure reservoir and treat reflex incontinence. Botulinum toxin injections are a promising alternative. Electrical neuromodulation is not a first line treatment for neurologic bladder as yet but its role may grow in future. Intravesical electrical stimulation is the only available option to induce/improve bladder sensation and enhance micturition reflex in neurologic hyposensitive and hypocontractile detrusor.

Surgical treatment can be indicated if conservative treatment fails. Sacral anterior root stimulation combined with posterior rhizotomy can restore bladder function in selected spinal cord injured patients with treatment refractory detrusor overactivity. Transurethral sphincterotomy is an option to adequately drain the bladder in spinal cord injured male patients. Injections of botulinum toxine in the sphincter can be an alternative. Enterocystoplasty has passed the test of time in achieving a low pressure reservoir but complications and reinterventions are not rare. Neurological decentralization has been most successful with sacral rhizotomy. Increasing urethral resistance in patients with good bladder capacity and compliance but stress incontinence is surgically mostly done with the implantation of an artificial urinary sphincter, though a sling procedure may be an alternative assuming that CIC can be done. Though less frequently used, after failure of other treatment options, continent or non continent urinary diversion can be needed. More results are awaited from research in bladder reinnervation techniques.



THE EMERGING ROLE OF THE CONTINENCE SPECIALIST NURSE

Mandy Wells

In a number of countries especially the UK, Australia, Canada and New Zealand the role of the Continence Specialist Nurse is embedded and recognised as an important part of the whole patient package of Continence Care.

In other countries including Taiwan, Malaysia, Japan, Brazil and the Scandinavian countries it is a role that is starting to develop.

The key concepts of a Specialist Nurse are clinical (working on a day to day basis with patients), education and training, audit and service development. Specialist Nurses should also be autonomous practitioners.

This latter does not however happen in some countries where specialist nurses are sometimes seen as the "doctors' handmaidens" and only provide care prescribed by Medical Practitioners. This model is starting to change as more nurses are getting the academic qualifications and expertise in order to be able to say that they can diagnose and prescribe management and treatment strategies as autonomous practitioners.

In addition to this in some countries the role of the autonomous nurse specialist is actively discouraged as medical professionals get their income from carrying out procedures that are paid for by insurance companies.

Despite these issues there are countries that are modelling themselves on the model originally conceived in the UK of the autonomous nurse specialist post.

Today in the UK there are over 600 Nurse Specialists (and 10 Nurse Consultants who are equal in authority to a Medical Consultant).

These nurses can prescribe and teach Pelvic Floor Exercises, Bladder Retraining, Lifestyle changes, Electrical Stimulation, Biofeedback, Intermittent Catheterisation and are now prescribing the whole range of medications that are required by people with lower urinary tract problems as well as concurrent bladder problems. They see all age groups from 3-103!

The key to these roles working is that nurses, medical practitioners and Physio therapists work hand in hand to develop clinics and services that meet the needs of their patients as well as their own specialist interests and competencies. This is complex and can lead to some initial rivalry. However, models of multi-professional practice are emerging which show how beneficial this joint working can be. In the UK there is even a name for such services this being "Integrated Services". Such services include specialist nurses within primary and secondary care as well as their medical, surgical and therapist colleagues.

The importance of a leading nursing voice in the speciality is not only occurring in the UK but Canada and Australia are appointing similar roles to those of the Nurse Consultant who is the local lead for the provision of continence care. This has of course been done with the agreement of local medical and therapy practitioners.

The world of acknowledgement of continence problems and their impact on the lives of the individual are growing and as well as the countries already mentioned there are embryonic attempts being made in some countries e.g. Spain, Italy, Greece to develop similar roles.

The Continence Nurse Specialist role is definitely emerging of one of credibility on the International Continence stage.

ASSESSMENT OF THE PELVIC FLOOR MUSCULATURE

Marijke Slieker-ten Hove

PELVIC FLOOR PHYSIOTHERAPY AND PELVIC ORGAN PROLAPSE

Pelvic Organ Prolapse knows a high prevalence among women. Studies showed prevalences of 35-40 % with stage 2 or more (Swift et al. 2002, Slieker et al. 2004).

The term prolapse was first used by Benedetti in 1497 to describe complete uterovaginal prolapse. As long as we know about prolapse as long many people tried to find therapeutical options to treat pelvic organ prolapse. In the early days of Hippocrates succession (vigorous shaking) was suggested as a method of treatment. The patient was tied up on a ladderlike frame and was shaken up and down during 5 to 10 minutes. The force of gravity and the shaken motion were thought to be restoring the prolaping organs back in place. He was also the first to put in the vagina a half pomegranate apple soaked in wine to create vasoconstriction in the vagina and create a mechanical block.

In conservative treatment of prolapse mechanical blocking of the vagina was the most popular treatment from the time of Hippocrates till the 1800 century. Van Roonhuysen of Holland first described in the 1600s vaginal vault prolapse and suggested pessary treatment. In the nineteenth century many conservative treatments were available for pelvic organ prolapse, including different intravaginal pessaries. However, such treatments as cold water douches, hip baths and vaginal lavations and surf bathing were recommended as well as uterine gymnastics and massage (Emge and Durfee, 1966, Nieminen, 2004). In 1948 Arnold Kegel first suggested to train PFM to treat stress-incontinence by developing power of the muscles and stronger contraction reflexes to compensate the intra abdominal pressure.

The term pelvic floor dysfunction has mostly been connected to prolapse of pelvic organs, meaning a disfunction of the connective tissue and ligaments. However the pelvic floor consists also of muscles, which close the pelvic outlet pierced by the rectum, vagina and urethra through genital hiatus. The pelvic diaphragm is mainly composed of the levator ani and coccygeus muscles. Between the coccyx and the anus the levator muscles fuse to form a firm, muscular plate called the levator plate. The tonic contraction (constant) of the puborectalis muscle, part of the levator-ani-complex, closes the urogenital hiatus and contributes to the horizontal axis of the proximal vagina and levator plate (Strohbehne, 1998).

In a woman in upright position, without prolapse, the proximal vaginal axis is nearly horizontal, lying on the parallel levator plate. Studies have shown that as intra-abdominal pressure increases, the pelvic diaphragm contracts and maintains the position of the levator plate and horizontal vaginal axis. (Nichols et al. 1970, Harris and Bent 1990, Nicols 1992, Raz et al. 1993) As a consequence, the uterus, vagina and rectum are pushed against the levator plate, but not through the genital hiatus.

Connective tissue and striated muscles maintain the support of the posterior wall (DeLancey, 1999). Contraction of the levator ani muscles closes the vagina and relieves the connective tissue of constant load and with normally functioning levator ani muscles, no stress will occur on the midvaginal support (DeLancey 1992a)

The aetiology of the various types of POP is widely thought to be similar. The range of etiologic factors includes congenital weakness of tissues, parity, ageing, lifestyle, COPD, smoking. The most significant being advancing age and parity (Nichols 1992, Mant et al. 1997, Samuelsson et al. 1999, Swift, 2000)

Labor and vaginal delivery are significant initiators in the development of POP. They contribute by damaging connective tissue, nerves and muscle fibers. Neuromuscular damage seems to be the most important factor (DeLancey 1993). Also the pregnancy itself seems to be a riskfactor for POP regardless the mode of delivery (O'Boyle et al. 2002). Also the role of the size of the genital hiatus is playing an important role, at least in the recurrence of POP after surgery (Vakili, 2005). Any condition leading to raised abdominal pressure renders an individual liable to an elevated risk of POP. This includes heavy work, COPD and obesity (Nichols, 1992, Mant et al. 1997). Rectocele shares the aetiological factors similar to those underlying other forms of POP. Factors in this particularly area include excessive training due to constipation or non-relaxing puborectal muscles (Segal and Karram, 2002).

The intra abdominal pressure seems to play an important role in developing and/or worsening POP. When connective tissue and reflexcontraction of the PFM are not able to control the location of the pelvic organs there must be a possibility for the striated musculature to create some effect. Striated muscles can be contracted conscious and therefore can be trained with different options. Although observed in a small group PFM also seem to contract in voluntary or reflex co-activation with abdominal muscles (Sapsford et al., 2001). Some patients present a dysfunctional co-contraction between PFM and abdominal muscles.

When the patient squeezes or coughs, a caudal displacement of the pelvic floor can occur. This displacement is well known but is this due to weakness or to coordinative incapacity? Before starting up any treatment this needs to be found out in the diagnostic process of the physiotherapist.

Should the physiotherapist focus on strengthening or coordination? What will be the most effective? And when will be the best period to train: preventive, pre- or postpartum. Pre- or post-operative? The study of Devreese from 2004 encouraged to involve coordinative aspects in the PFM training.



In the study of Slieker et al. (2004) a relationship of the function of the PFM and POP was shown. In this study the force was not significant related to POP, but in the unconscious and coordinative aspects of the PFM function high significant differences were shown between stage 0 and stage 1.

The group of stage 0, according to the POPQ staging, 23.8 % presented a perineal descent during coughing versus 61.9 % in stage 1. The same was shown when forcing celes were observed during coughing. 0 % in stage 0 versus almost 26 % in the stage 1 group gives significant different outcomes.

Miller and her group (2000) showed that a PFM contraction in preparation for, and throughout, a cough can augment proximal urethra support during stress, thereby reducing the amount of dorsocaudal displacement. In this study, she demonstrated also women's ability voluntarily to augment a normal levator ani muscle contraction or to accomplish a conscious contraction if the normal mechanisms generating it during a cough have been lost. If PFM training in all aspects can be helpful to reduce surgery, complaints and recurrences, is still not proven and needs to be studied.

Because the prevalence of POP is high in women and the amount of surgery in a woman's life can go up to 2-3 times it is relevant to study the process of prolapse of the pelvic organs and the damaging factors trying to find good moments and options to start training PFM to influence the POP process.

Despite the many different procedures available for correction of POP, surgery is associated with a high risk of recurrence of prolapse. Recurrence rates are quoted as high as 30% (Olsen et al., 1996), with higher rates associated with specific procedures (Kholhede et al. 1997, Mant et al., 1996, Clark et al., 2003).

References

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AGEING OF THE PELVIC FLOOR

Diaa E. E. Rizk

Background / Objective

Despite the prevalence and detrimental effect of urinary and fecal incontinence on many postmenopausal women, there seems to be no consensus at present on the exact underlying mechanism. The theory that low circulating estrogen is causally related to these disorders is not based on any supportive evidence. It is not also clear whether normative ageing is primarily or secondarily responsible.

Laboratory animals which are old and those with surgically-induced ovarian failure provide the unique opportunity to investigate the role of these 2 specific biological conditions (menopause and ageing) on the pelvic floor structures circumventing several extrinsic variables inherent in clinical studies. The anatomy of these structures in rats is sufficiently similar to that of humans to serve as a model for experimental studies. Fisher 344 rats are particularly suitable for ageing research because the mean survival time of animals in this colony is prolonged (30 months) compared to other rat models. The experimental evidence of ageing of the pelvic floor will be reviewed.

Methods

The most common surrogate biomarkers studied to assess the effects of ageing and/or estrogen deficiency on the pelvic floor were morphological: the amount and relative proportion of submucosal collagen fibers types I and III in the urethra and anal canal and of isomyosin fibers types I and II in the striated pelvic floor muscles using Western Blot analysis as well as the number of submucosal vascular plexuses in the urethra and anal canal using light microscopy. Measurement of cytoplasmic expression of p27^{kip1} in the striated pelvic floor muscles by Western blot analysis is also recently considered a specific biochemical marker of pelvic floor ageing because this protein normally regulates muscle cell differentiation and apoptosis.

Results

Most studies showed anatomical, histological and ultrastructural evidence of derangement of structure of the female pelvic floor with the cumulative effect of menopause and ageing. All biomarkers of pelvic floor ageing studied were significantly increased in old compared to young-adult female rats. Ovariectomy significantly increased these changes further in old versus young-adult rats with either smaller or larger differential effect on some pelvic floor structures than ageing compared to young-adult animals. The effects of ovariectomy in old rats were not totally reversed by estrogen replacement suggesting an independent ageing effect.

Conclusion

Ovariectomy and subsequent estrogen deprivation exacerbates the inherent ageing changes in the pelvic floor of old rats indicating a synergistic, deleterious and independent interaction between hypoestrogenism and normative ageing. Studying the individual contribution of biological versus reproductive senescence to ageing of the pelvic floor in animal models may assist in identifying therapeutic strategies to delay this inevitable process.



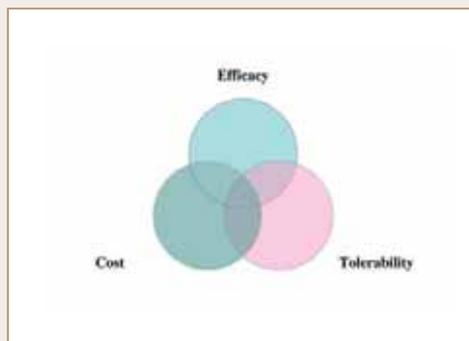
MY DRUG IS BEST FOR OAB: TOLTERODINE (Pfizer)

Tony Smith

Tolterodine

What is Tolterodine?

- A tertiary amine antimuscarinic
- It combines both M2 and M3 activity
- The ratio of M2 and M3 receptors in detrusor muscle is 80:20
- Tolterodine is highly bladder-selective compared with the salivary glands
- It has relatively low lipophilicity



and thus may be of more benefit than agents that are selective for M3
 Study showed salivary effects at 1 hour but bladder effects for 5 hours.
 Relatively low lipophilicity account for it limited CNS side effects.

Chess-Williams R. *Expert Opin Ther Targets* 2004;8(2):95-106.
Nilvebrant L, et al. *Eur J Pharmacol* 1997;327(2-3):195-207.
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Cost?

Per Month

- Propiverine £61.12
- Solifenacin £35.91
- **Tolterodine £29.03**
- Trospium £26.00
- Oxybutinin £24.68

Tolerability

- Meta analysis of antimuscarinics
 - Tolterodine ER had the most favourable tolerability profile.
 - 29% lower incidence of withdrawal than in patients treated with placebo.

Meta analysis Chapple et al 2005
 Compliance is important ----in an epidemiological study conducted by Milson et al 2001 found that of all those who saw a physician for OAB only 27% currently on treatment.

Tolerability

Clinical Study	Study Duration (wk)	No. of Patients	Patient Continuation Rate
Van Kerrebroeck, et al	12	507	96%
Kreder K, et al	52	1077	71%
STAT	12	1138	80%
MERIT	8	854	95%

How to assess efficacy?

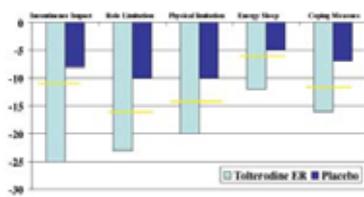
OAB

Urgency, with or without urge incontinence, usually with frequency and nocturia.

- Long term data
- Clinically relevant end points

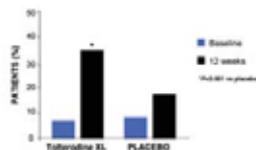
We must avoid making what is measurable important and find ways to make the important measurable.
Care taken in interpreting RCT comparing new and "old" drugs– Percentage "Naïve Patients" to the drugs are rarely stated. Patients may have already failed treatment on the "old" drug.

Long term improvement: KHQ



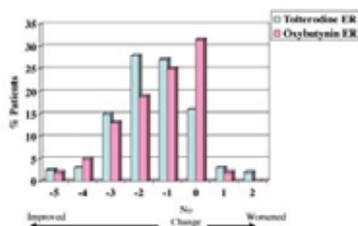
12 months
Bars represent Minimal Important Difference Scores determined by Reese et al Qual life Res 2003
Kelleher et al Am J Manage Care 2002

Ability to finish a task

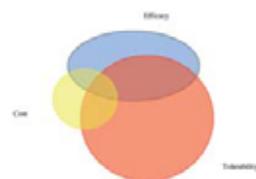


SIXFOLD INCREASE IN ABILITY TO FINISH TASK BEFORE TOILET VISIT compared to placebo
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Change in Bladder Condition



Summary





MY DRUG IS BEST FOR OAB: OXYBUTYNIN (Janssen Cilag & Aspen)

Hassan Shaker

Oxybutynin chloride is the golden standard for pharmacotherapy of the overactive bladder. This medication is the only one that stood the test of time and passed it with flying flags. There are many points that render this drug the best for treatment of OAB. First is its safety. This medication has been around for several decades. It is one of very few medications that have been approved for treatment of overactive bladder in children and infants. None of the side effects that have been reported during this period is life threatening or major. Most of them are related to the anticholinergic mode of action. These are: mouth dryness (87%), somnolence (40%), blurred vision (17%), constipation (31%), dizziness (38%), impaired urination (29%), nervousness (23%), and nausea (17%).¹

The most unique about this medication is its versatility in its route of administration. It can be administered orally either in a tablet form or in a syrup form. The long acting oral oxybutynin did not only provide the convenience of only one tablet daily dosage, it also decreased the side effects owing to the steady blood level of the drug preventing the peaks and dips seen in the immediate release form which is partially responsible for the side effects. Furthermore, most of the drug is released in the distal gut avoiding the proximal part which directly drains to the portal circulation leading to hepatic metabolism of the drug and release of the metabolites responsible for the anticholinergic side effect.² Intravesical instillation is one of the preferable routes for treatment of patients with overactive bladder who are on CIC. The beauty of this route is that the medication bypasses hepatic and gastrointestinal metabolism which yields most of the metabolites that are responsible for most of the side effects namely N-desethyloxybutynin (N-DEO). There is a new investigational device that is placed intravesically and release the medication for a whole month. Such device, if proves to be effective, can extend the intravesical route to include patients other than those on CIC. The transdermal route is a very promising one. It shares the intravesical route in its minimal side effects by avoiding hepatic and gastrointestinal metabolism of oxybutynin. Head to head comparison with other newer medications have shown that there is no difference in the efficiency of these newer agents as compared to the oxybutynin.³ immediate release though some of them showed fewer side effects.^{4,5,6} Nevertheless, when these medications were compared to the extended release form or the transdermal system, no clear benefit of these drugs was seen.

At this point in time, oxybutynin is still the golden standard among pharmacological agents treating OAB against which, all newer medications are compared. Until these new medications prove that they are more effective than oxybutynin and beat the unbeatable safety records of this medication, it will stay the best drug available for treatment of overactive bladder.

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MY DRUG IS BEST FOR OAB: SOLIFENACIN – VESICARE (Astellas)

Hashim Hashim

Solifenacin has been marketed in Europe and North America for the treatment of OAB. It has recently been marketed in the Middle East as well. It is an oral antimuscarinic drug administered once daily in 5mg or 10mg doses.

Solifenacin is 10-times more selective for the M1 and M3 receptor subtypes than the M2 subtype and has selectivity for the bladder over the salivary glands. The mean time to peak plasma concentration (C_{max}) is 3–8 hours. The mean elimination half-life (t_{1/2}) is 45–68 hours. Steady state is achieved in approximately 10 days. The pharmacokinetics are not affected by food. It is primarily metabolised by the liver (CYP450 3A4) resulting in one active and three inactive metabolites and is excreted in urine (70%) and faeces (23%).

A few large multi-centre, multinational, double-blind, placebo controlled clinical trials have been conducted with Solifenacin and they have been published either in paper or abstract form. The main study is the STAR study which was Solifenacin in a flexible dose regimen with Tolterodine XL as an Active comparator in a double-blind, double-dummy, Randomised overactive bladder symptom trial.

The objectives of the STAR study were to assess the efficacy, safety and tolerability of a flexible dose regimen with solifenacin succinate 5mg or 10mg (2 x 5mg) od compared with tolterodine 4mg od in patients with overactive bladder symptoms.

The results of this trial showed that Solifenacin (combined dose) was non-inferior and not superior to tolterodine in reduction of daytime frequency and nocturia. It was however superior in terms of reduction of urgency, urgency incontinence, number of pads used and in increase of voided volume and improvement in patient perception of bladder condition. In other studies, it has also been shown to be useful in mixed urinary incontinence and in increasing the warning time and improving quality of life.

The majority of side effects (dry mouth, constipation, blurred vision) were mild to moderate with less than 5% withdrawal rate, although overall, may be slightly higher than tolterodine.

Solifenacin is contraindicated in patients with urinary retention, severe gastrointestinal conditions (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma. It is contraindicated in moderate hepatic impairment and severe renal impairment if patients who are also receiving a potent CYP3A4 inhibitor such as ketoconazole.

In the UK, the overall cost of solifenacin treatment within a practice or hospital depends on how many individuals receive the higher dosage strength. The 5mg tablets cost £25.78 for 28 days, which is cheaper than tolterodine 4mg XL, but the 10mg tablets are more expensive at £33.53 for 28 days.



MY DRUG IS BEST FOR OAB: PROPIVERINE (Apogepha)

Helmut Madersbacher

PROPIVERINE – WHAT ARE THE MARKETING MESSAGES?

Propiverine, in contrast to other drugs indicated for detrusor overactivity, comprises a dual mode of action with neurotropic and muscolotropic properties (Madersbacher & Mürtz, 2001). Efficacy has been proven in numerous studies conducted in Europe and Japan in Caucasian and Japanese / Korean patients covering a broad range of different indications: symptoms of the OAB, idiopathic and neurogenic detrusor overactivity in adults, idiopathic and neurogenic detrusor overactivity (myelomeningocele) in children. In elderly men with OAB and concomitant BPE/BPO propiverine and alpha-adrenoceptor antagonists were administered together.

In OAB propiverine and tolterodine are equieffective as was shown in a head-to-head study in adults (Jünemann et al., *European Urology*, 2005). Furthermore, propiverine and tolterodine are equally tolerable. Furthermore, in long-term studies it was proven that adverse events decreased during the time-course following propiverine treatment (e.g. Madersbacher et al., *ICS* 2005). In unobstructed and obstructed male patients with OAB and BPE/BPO no clinically relevant increase of post-void residual, no acute urinary retention was observed (Lee et al., *Journal Urology*, 2005).

PROPIVERINE: WHAT IS THE SCIENTIFIC BASIS FOR THESE MESSAGES ?

A complex dual mode of action is based on the parent drug propiverine hydrochloride comprising antimuscarinic and calcium²⁺-modulating properties. Three major main metabolites were detected, the N-oxide is the main metabolite. In the experimental setting only the combination of atropine (antimuscarinic) and nifedipine (Calcium-channel blocker) achieved an extent of detrusor inhibition which was comparable to that of propiverine. In preclinical studies (in-vivo studies in the mini-pig) propiverine and tolterodine induced an equivalent decrease of salivation, thus suggesting comparable tolerability of both drugs also in humans (Scheepe et al., *Aktuelle Urologie*, 2000).

PROPIVERINE – WHAT IS THE DOCUMENTATION FOR THESE MESSAGES?

In regards to idiopathic detrusor overactivity Jünemann and coworkers (*European Urology*, 2005) showed in a head-to-head study that the increase in maximum cystometric bladder capacity following propiverine and tolterodine was comparable. Also in regards to tolerability there was no difference between these two drugs, as was evidenced with respect to the overall adverse event incidence rate and with respect to the incidence rate of dryness of the mouth.

In regards to CNS adverse events cognitive, mental and motor functions in elderly patients with various neurological diseases (multiple cerebral infarction, M. Parkinson, M. Alzheimer) were not negatively affected during a 8-week treatment with propiverine (Uchiyama et al., *ICS* 2005).

In regards to neurogenic detrusor overactivity in a placebo-controlled study (Stroher et al., *Spinal Cord* 1999) again the maximum cystometric bladder capacity increased, the maximum detrusor pressure amplitude during voiding decreased significantly following propiverine treatment compared to placebo.

Tolterodine, trospium, darifenacin and solifenacin are not registered for the use in children and only very few studies with these drugs are published. Additionally, oxybutynin has traditionally been used in children (Hehir & Fitzpatrick, *European Urology* 1985), however numerous reports evidenced an unfavourable adverse event profile. Propiverine, registered for the use in children in Germany and some other countries, exerts significantly less adverse events compared to oxybutynin according to a very broad paediatric data base (Marschall-Kehrel et al., *Journal Urology* 2004, Madersbacher et al., *European Urology* 2006, Alloussi et al., *European Urology* 2006). Therefore, propiverine proved to be significantly better tolerated compared to oxybutynin also in children suffering from idiopathic or neurogenic detrusor overactivity.

In several studies in men with OAB and concomitant BPE/BPO alpha-adrenoceptor antagonist monotherapy was compared to the combined usage of an alpha-adrenoceptor antagonist and propiverine: this combination regimen achieved higher rates of improvement in OAB-symptoms. In only one out of four studies 2 out of 75 patients (Saito et al., *Japanese Journal Urology Surgery* 1999) experienced urinary retention.

The advantages of a propiverine extended release formulation compared to the propiverine immediate release formulation have been shown, especially with respect to a further improved tolerability profile (Jünemann et al., *ICS* 2004).



MY DRUG IS BEST FOR OAB: PROPIVERINE (Apogepha) (Cont.)

WHY IS PROPIVERINE THE BEST DRUG FOR OAB?

Propiverine is unique in regards to its dual mode of action. Numerous placebo- and/or reference-controlled studies as well as open-label studies evidenced excellent results in the following patient populations: idiopathic detrusor overactivity and neurogenic detrusor overactivity, both in adults and in children. Especially for children a dose formulation containing 5 mg propiverine (Mictonetten™) has been designated. In men with OAB and concomitant BPE/BPO very promising results were achieved by combining alpha-adrenoceptor antagonists and propiverine.

In conclusion, propiverine comprises an excellent efficacy and tolerability profile, it is the market leader in Japan. However the marketing possibilities are according to a medium-sized family-owned company.

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MY DRUG IS BEST FOR OAB: OXYBUTYNIN PATCH (UCB Pharma)

Linda Cardozo

Oral Oxybutynin has been used for many years in the treatment of overactive bladder syndrome (OAB). Its principal action is to block M3 muscarinic receptors, reducing detrusor contractility. However oxybutynin is also active against muscarinic receptors in the salivary glands, leading to an unacceptably high rate of dry mouth.

Problems with antimuscarinic side effects such as dry mouth, have led to the development of alternative agents and formulations. These include extended release oxybutynin, marketed as Ditropan or Lyrinel XL, and newer anticholinergics such as Darifenacin and solifenacin. All oral formulations of anticholinergics are subject to extensive hepatic and gastro-intestinal pre-systemic metabolism. Oxybutynin is rapidly metabolised to N-desethyloxybutynin.

This reduces bioavailability, and leads to troughs and peaks in drug concentration following administration.

Transdermal formulations of other drugs have been available for almost 25 years. They are popular with patients, and are used for a range of medications requiring continuous release, including oestradiol, fentanyl, and nicotine. This route of administration helps avoid first-pass metabolism, stabilising drug concentrations. The lower drug concentrations lead to a reduced rate of dose-related side effects, while maintaining therapeutic blood levels. The combination of fewer side effects and ease of administration increases patient compliance with therapy.

Oxybutynin is now available in a matrix-type transdermal patch, for twice weekly administration. It is marketed as Oxytrol or Kentera. The licensed dose is a 36mg patch, releasing an average of just 3.9mg oxybutynin/24 hours.

One Phase II study demonstrated that transdermal oxybutynin has equivalent efficacy, on both objective and subjective measures, to oral immediate release oxybutynin (max 20mg od). The incidence of anticholinergic side effects was much reduced, with 89% of patients reporting, "none", or "mild" effects only.

A further Phase III study has shown that transdermal oxybutynin and extended release tolterodine (4mg od) are associated with equal improvement in incontinence episodes, urinary frequency, mean voided volumes, and incontinence specific quality of life scores, with statistically significant benefit compared with placebo. Although these trials are powered only to detect a difference in efficacy, the rate of anticholinergic side effects is no higher for transdermal oxybutynin compared with placebo.

In common with other transdermal systems there is an associated rate of erythema and pruritus (up to 14%). These separate adverse effects may limit compliance in some patients.

Transdermal oxybutynin is a novel treatment for OAB, with significant benefits compared with existing oral medications. It offers the efficacy of these established anticholinergics, with an unprecedented low rate of adverse anticholinergic effects. Were cost not an issue, the combination of efficacy and acceptability should make it an obvious choice as a first line treatment for OAB.

NEUROUROLOGY UPDATE

Helmut Madersbacher

In their foreword to the book “Neurourological Urology” E. Bors und A.S. Comar (1971) stated that Neuro-Urology can only be understood by combining thoughts and methods of Urology, Neurology, Neurosurgery, Psychiatry, Traumatology and Rehabilitation Medicine.

The following topics will be discussed, Progress (1) in understanding physiology and pathophysiology of the lower urinary tract, (2) in diagnosis and (3) therapy of neurogenic lower urinary tract dysfunction and I’ll finish with (4) some ideas on the future of Neuro-Urology.

Pathophysiology

In the 1960’s we only knew that via pathways from the CNS to the bladder bladder contractions are induced by activating cholinergic receptors, about 10 years later also the afferent reflex pathway became more evident, during the next decade it was realized that normally the afferent input from the bladder to the CNS is conducted in myelinated A- δ fibres. But to convey afferent input under pathological conditions, e.g. after spinal cord injury, C-fibres are activated. It became clear, that such receptors can be blocked by intravesical instillation of capsaicin and resiniferatoxin, thus relaxing the overactive detrusor. During the last 8 years much attention was paid to the urothelium, which is not just a barrier, but functions as a metabolic organ: it releases e.g. NO, ATP, Acetylcholin, expresses many receptors, incl. M2- and M3, and communicates extensively with the underlying structures.

Much of our understanding of cerebral structures to be involved in micturition and withholding micturition we are owing to 15 young volunteers, who were trained to achieve micturition by lying supine in the tube of an MRI. Blok and Holstage initiated these investigations in 1997. On the basis of these MRI studies it was confirmed, that there is a pontine micturition center in the dorsal pons (M-region) and that the pontine center for the external sphincter is located more laterally (L-region). They also found that afferent input from the periphery projects firstly to the periaqueductal grey and from there ascending pathways originate to cortical and subcortical centers and descending neurons inhibit or stimulate the pontine micturition centre.

Own investigations in patients with Parkinson’s disease revealed that with increasing duration and increasing severeness of the disease neurogenic detrusor overactivity occurs causing symptoms of the overactive bladder including overactive detrusor incontinence. The way this functions was elegantly shown by Seiff and co-workers from Kiel in 2003 on the example of Parkinson patients, who have received an implant for deep brain stimulation (SDN). Urodynamic studies with the brain stimulator on and off enlightened the inhibiting influence of the basal ganglia on the detrusor reflex: STN stimulation normalizes detrusor hypersensitivity in Parkinson patients, thus proving the concept of increasing detrusor overactivity with increasing severeness of the disease.

Functional MRI is able to detect structures involved in the cortical and subcortical control of bladder and sphincter: according to Reitz and co-workers, from Prof. Schurch’s department, repetitive voluntary pelvic floor contractions with a full and an empty bladder activated areas known to be involved in the control of the bladder, they activated supplementary motor areas as well as the basal ganglia, confirming that pelvic floor contraction, which is recommended for inhibiting the urge to void, really inhibits detrusor activity centrally. This proves that the clinical effect of such manoeuvres is not only a mechanical one by occluding the bladder outlet.

Diagnosis

New techniques in the field of diagnosis allow to define the dysfunctional pattern in the individual patient, moreover they also improved considerably our knowledge on neurogenic lower urinary tract dysfunction.

In regards to diagnostic procedures video-urodynamics are the State-of-the-Art to evaluate the underlying pathophysiology, for follow-up urodynamics may be sufficient depending on the individual situation. With the help of these investigations we are able to define various dysfunctional patterns of detrusor and sphincter.

Neurophysiologic testing gives additional information on the function/dysfunction especially of afferent nerves: We have focused on the electrical stimulation of the bladder neck area, to prove whether electrical stimulation is able to evoke cortical potentials, allowing a judgement on the afferent activity at least to exteroceptive stimuli. The results of this investigation are extremely helpful, when it comes to the indication of intravesical electrotherapy, which only works in patients, in whom at least some afferent fibres to the cortex are still functioning (see below).



We do know that only (video-)urodynamics can detect risk factors within the lower urinary tract, before they cause upper urinary tract damage.

In regards to follow-up (video-) urodynamics one may ask "how early is too late, however, the intervals have to be based on the risk factors being present as well as on the individual situation of the patient.

Therapy

The aim of therapy in lower urinary tract dysfunction still is to preserve the kidney function and to control incontinence possibly to restore continence. Since about 20 years the therapy of choice to treat the spinal reflex bladder, according to the new terminology of the ICS, now called neurogenic (spinal) detrusor overactivity, is (1) to relax the overactive detrusor for controlling a high pressure situation during the storage (Low Compliance) and the emptying phase, mostly combined with (2) intermittent catheterisation to circumvent unbalanced voiding due to detrusor-sphincter-dyssynergia (DSD). This concept replaced the area of transurethral sphincterotomy, which was inaugurated in 1958 by Ross et al. in the U.K. Transurethral sphincterotomy also nowadays has its place especially in the high tetraplegic man when intermittent catheterization is not possible. A good sphincterotomy - although re-sphincterotomies are necessary in about 40 % of our patients - guarantees preservation of the upper urinary tract in the vast majority, however, continence can not be achieved and a condom urinal is necessary.

Suprapubic triggering to empty the bladder is risky and should only be allowed if the urodynamic situation is safe. Basically it should be replaced by intermittent catheterisation.

Intermittent catheterisation (IC) was introduced by Sir Ludwig Gutmann in Stoke Mandeville for bladder emptying during the spinal shock phase already in the late 50's and was popularized on the other side of the Atlantic ocean by Jack Lapides. He recommended the clean technique also for long-term bladder emptying. The experience, that IC really works also for long-term treatment, with an acceptable rate of urethral pathology and a low rate (3 %) of strictures needing treatment, was one of the greatest progress Neuro-Urology has made during the last 25 years, enabling also adequate bladder emptying e.g. in augmented bladders and bladder substitutes. In most European countries aseptic IC is used, in other area of the world clean IC is practised.

With the combination of IC and detrusor-relaxing therapy, with anticholinergics as the first line treatment, intravesical pressures can be controlled and continence be achieved in these patients in about 70 %. In some centres, e.g. in New Zealand, and other areas of the world, there is a tendency to replace intermittent catheterisation by long-term suprapubic catheterisation, last but not at least due to economic reasons. Despite some optimistic reports, most neuro-urologists believe that a permanent suprapubic catheter can not be the solution for the future. However, a few patients may benefit from it.

If anticholinergics are not effective enough or are not tolerated in adequate dosages, the second choice nowadays is the injection of Botulinum Toxin A into the bladder wall. The European study, inaugurated by Prof. Schurch, in which our unit also participated as well as a recently published placebo controlled study, have proved the efficacy of this new therapy. The effect of Botulinum Toxin in the smooth muscle detrusor lasts much longer than in the striated muscles for reasons we do not know. In the mean after nine months the injections have to be repeated.

Botulinum Toxin has been introduced into Neuro-Urology to relax the spastic external striated sphincter in patients with DSD, at least temporarily. This pharmacological sphincterotomy can be used as a test procedure to see what happens when a surgical sphincterotomy is planned, especially in patients, with a danger for incontinence in so far continent patients. Although it is not the topic of this lecture, I would like to mention, that instillations of Botulinum Toxin in the bladder have shown to be useful in interstitial cystitis and moreover, injections into the prostate cause apoptosis in the enlarged prostate: the size of the prostate decreases and obstructive micturition symptoms improve. Therefore the indications for Botulinum Toxin may become several and this substance, still the most poisoning substance on earth, may become something like the penicillin of the 21st century for the neuro-urologist.

Before the era of Botulinum Toxin the alternatives, if oral anticholinergics were not effective, were either intravesical instillation of vanilloids like e.g. capsaicin or resiniferatoxin or surgical procedures, e.g. sacral deafferentation (posterior sacral root rhicotomy) or bladder augmentation. In regards to vanilloids capsaicin is more or less out already due to the side effects.

Resiniferatoxine has proved to be effective also in the spinal reflex bladder, however the substance is not registered for human medicine and can therefore only be applied within studies. Sacral deafferentation is an elegant method: One has to cut all posterior roots from S2-S5 on both sides.

NEUROUROLOGY UPDATE (Cont.)

The results to achieve detrusor acontractility are excellent and lasting, however there are major disadvantages: the procedure is destructive, and patients are more and more reluctant when nerves are cut, even if they are not useful for them. Moreover with sacral deafferentation they lose any sensation also for the bowels and constipation may be increased unless defecation can not be achieved by electrical stimulation by simultaneous implantation of a sacral anterior root stimulator. In the era of BotulinumToxin the indications for sacral deafferentation have become less.

Although IC is nowadays the state-of-the-art to empty the neuropathic bladder, some patients can not do it, some patients have nobody who can do it for them and some do not accept this type of bladder emptying.

For those with an intact sacral reflex arc, at least on the efferent side, sacral anterior roots stimulation (Brindley) is an option and mostly combined with sacral deafferentation. Based on his profound knowledge of neuro- and muscle physiology Prof. Giles Brindley in London designed stimulation in bursts with intervals in between: during stimulation sphincter and detrusor are activated, however during the interval the quickly reacting striated sphincter relaxes immediately while the slowly reacting smooth muscle detrusor stays still in contraction. Thus "post-stimulus" voiding is achieved. Although not ideal this technique has excellent results with a long-term efficacy in 85 % after mean observation time of 10 years.

Sacral neuromodulation comprises (1) percutaneous nerve stimulation as a test period, during which the electrodes are placed to the relevant sacral roots - mostly S3 giving the best response - and are then connected to an external stimulator. If the test period reveals sufficient efficacy, in a second stage the stimulator (IPG) is implanted. Sacral neuromodulation results in detrusor relaxation, but at the same time also dysfunctional voiding may be improved. The results with this method in neurogenic lower urinary tract dysfunction are somewhat controversial.

For the combination of an acontractile detrusor with an acontractile (incompetent) sphincter, typically for conus-cauda-lesions, bladder expression by Valsalva or CredÉ has been used extensively. Due to the high intravesical pressures, created this way, associated with an enormous risk for upper urinary tract damage by vesico-uretero-renal reflux this method should only be used if urodynamically safe. Otherwise intermittent catheterisation should be performed or the patient persuaded to do it.

About 15 years ago, a sophisticated method was recommended to express the underactive detrusor with the help of a Latissimus dorsi muscle transfer: The latissimus dorsi muscle was wrapped around the bladder in a way that contraction of the latissimus dorsi squeezed the bladder. The nerves were anastomized in such a way that the patient could be trained to contract the transferred muscle voluntarily. Press conferences and articles in the newspapers predicted enthusiastically "no more intermittent catheterisation for patients with a weak detrusor", thus creating, as we know nowadays, false hopes. It could only work if the outflow resistance is low or patients are able to relax the sphincter actively, but under these conditions voiding by Valsalva or CredÉ is mostly possible and patients do then not need a transferred Latissimus dorsi muscle.

Another attempt to empty weak neurogenic bladder is that of Prof. Chuan-Guo Xiaou, who recommends an artificial somatic-autonomic reflex pathway procedure for bladder control in children with spina bifida as well as in adults with neurogenic detrusor weakness: After limited laminectomy he performs lumbar ventral root (L 5) to sacral ventral root (S 3) microanastomosis; the dorsal L 5 root is left intact as the afferent branch of the somatic-autonomic reflex pathway after axonal regeneration. The bladder reflex is stimulated by scratching the skin of the L5 dermatome. Dr. Xiaou claims that the artificial somatic-autonomic reflex arc procedure is an effective and safe treatment to restore bladder continence and reverse bladder dysfunction. Interestingly enough, his method was published in the Journal of Urology only recently without any comment from the editors side, although the urodynamic curves published are really not convincing:

Instead of a weak but normal compliant detrusor a low compliance bladder is present postoperatively and voiding is achieved only by abdominal straining and not by detrusor pressure.

Intravesical electrostimulation is a method which is especially useful to improve/normalize the neurogenic



hyposensitive/hypoactive detrusor. The efficacy of this method is discussed controversially, however in studies with disappointing results no attention was paid to inclusion criteria, which comprise most importantly at least some intact afferent fibres present.

What is the future of Neuro-Urology? Where do we need improvements? Where do we need innovations? In regards to intermittent catheterisation we do need controlled studies possibly with the patient as his own control in order to prove whether this catheter or this technique is better than the other. Of course innovations are always welcome and one can imagine that a lipstick-sized catheter for female patients makes intermittent catheterisation more attractive and more acceptable. Pharmacological relaxation of the detrusor will focus in the future on the afferent side since we know that the urothelium does not only produce important neurotransmitters, but has also cholinergic M2 and M3 receptors. It really makes sense to inhibit the detrusor reflex where it starts and this is on the afferent side. The substance Nociceptin/Orphanin is a good example for this strategy. The traditional way to apply Botulinum Toxin into the detrusor is to inject it into 20, 30 or even 40 locations of the bladder wall. The concept to inject Botulinum Toxin only in the trigonal area, makes sense and the first experience with this technique are promising. Allergic reactions to Botulinum Toxin A, even when injected repeatedly, were not yet a problem, but could be overcome by using Botulinum Toxin B instead of the type A.

I have already mentioned the disadvantages of sacral deafferentation.

M. Craggs (London), replaced it by combining anterior sacral root stimulation with posterior sacral root neuromodulation, a procedure, which he called SPARSI. It is possible to suppress the overactive detrusor with sacral neuromodulation and at the same time to empty the bladder with the Brindley method, detrusor-sphincter-dyssynergia is still a problem, however it can possibly be overcome in the near future.

Another question is that of tissue engineering, or in other words, can cells seeded from a neuropathic bladder on a biomatrix replace a neuropathic bladder. Prof. Kropp from the University of Oklahoma has characterised the neuropathic smooth muscle cells in culture and has found that neuropathic smooth muscle cells have different characteristics in regards to contractility - decreased, cell proliferation - increased and cell adhesion -decreased, facts, which raises some concerns for current tissue engineering techniques for the neuropathic bladder. Nevertheless, further initiatives should focus on avoiding destructive surgery, to improve symptomatic treatment for compensation of deficits and to induce more restorative therapy.

So far, and in the near future, proper initial management of the bladder during the spinal shock phase, adequate bladder rehabilitation and life-long neurological care are still the keys to ensure an almost normal life expectancy for tetraplegics and normal life expectancy for paraplegics as well as a high quality of life despite neuro-urological deficits.

INJECTION THERAPY: BULKING AGENTS IN ISD

Sherif Mourad

Urinary incontinence following radical prostatectomy has a reported incidence of 5 to 12% [1]. Post-prostatectomy incontinence and other forms of male urinary incontinence have a significantly negative impact on Quality of Life. Urethral incompetence usually requires interventional therapy. Treatment of ISD in men after radical prostatectomy is a technically challenging procedure.

Surgical augmentation of intraurethral pressure includes slings and implants, such as artificial sphincters or periurethral bulking agents. The latter involves injection of a bulking agent at the area of the bladder neck and proximal urethra to enhance urethral resistance to urine flow by approximating the urethral mucosa.

The artificial urinary sphincter is a known effective solution in managing ISD. However, it carries the risk of disturbed bladder compliance and function to a degree that may affect the upper urinary tract. Moreover, there is the possibility of urethral erosion, especially in patients with a history of difficult pelvic operation and/or significant blood loss.

Complications such as infections and mechanical problems, requiring revisions are additional disadvantages. The sling operation is proving to be technically difficult in males, especially after radical pelvic surgery. Extensive fibrosis associated with male incontinence after surgery or trauma, and pelvic irradiation after radical prostatectomy further complicates the procedure, therefore, it is rarely performed.

Alternatively, injection or placement of a bulking agent has the advantages of being easily performed as an outpatient procedure because of the use of local anesthesia and a low complication rate, which makes it suitable especially in the elderly incontinent population.

Stress Urinary Incontinence (SUI), which is the involuntary loss of urine during stressful activities, develops in 10 to 30% of women of all ages [2]. In women, two types of sphincter abnormality are diagnosed, bladder neck hypermobility and Intrinsic Sphincter Deficiency (ISD). ISD may account for a higher failure rate of surgical procedures performed to treat Stress Urinary Incontinence (SUI) due to ISD.

Historically, slings have been the procedure of choice, however this procedure may increase and/or produce a significant incidence of urinary retention. Peri-urethral or trans-urethral bulking agents, which are less invasive, have been used to treat ISD for many years and avoid recurrent surgical procedures. Bulking agents are able to coapt the urethral mucosa and as a consequence produce higher resistance to increased abdominal pressure.

Injection of bulking agents into the urethral wall has been attempted with a variety of substances. The materials used to date have a wide range of success rates. The following are the so far studied agents:

Resorbable

Animal Origin - Bovine Glutaraldehyde Cross Linked Collagen
Human Origin - Fat
Chondrocytes (cell cultured, Reprogenesis Inc.)

Non-resorbable

Polytetrafluoroethylene (Teflon)
Silicone microimplants (Macroplastique)
Carbon particles (Durasphere)
Dextranomer and stabilized Hyaluronic acid (Zuidex)
Polyacrilamide Hydrogel (Aquamid)
Ethylene Vinyl Alcohol in Dimethyl Sulfoxide (Tegress)
Inflatable Silicon Balloons (ACT & ProACT)

Good results were reported with the use of polytetrafluoroethylene (PTFE) in the 1960s and 1970s [3]. PTFE (Teflon) paste consists of particles that vary in size from 1 to 100 μm , with 90% smaller than 40 μm , resulting in distant migration and granuloma formation [4]. The long-term results have been disappointing, Kiilholma and M%kinen reported that only 18% of patients were continent 5 years after polytetrafluoroethylene injection [5].

Collagen (Contigen) is expensive and may cause allergic reactions in around 3% of patients. In most studies incontinence returned gradually with a median continence duration of 23 months [6]. Repeat injections are necessary to achieve sustained continence, which increases the cost. The main disadvantages of using autologous fat relate to the variability of resorbtion as well as repeated injections. At 1-year follow-up only 28% of patients are cured with this therapy [7].



Numerous reports on PDMS for the treatment of female SUI have been published [8]. Encouraging results are reported in these studies, including 1 with over 5-year follow-up.

The Dextranomer is a type of sugar molecule that has been used for a number of years in the treatment of wounds. Hyaluronic acid is a naturally occurring substance produced by the body to firm tissues and lubricate joints. The hyaluronic acid used in ZUIDEX is synthetically produced. Neither of the ingredients in ZUIDEX gel is derived from animals, thus avoiding rejection risks that exist with animal-based products.

Aquamid is a Polyacrilamide hydrogel which is an atoxic, non-resorbable sterile watery gel. It is homogeneous, stable, not biodegradable, and has tissue-like viscosity and elasticity [9].

Tegress is Ethylene Vinyl Alcohol copolymer (EVOH) dissolved in Dimethyl Sulfoxide (DMSO) carrier. Upon injection, the DMSO carrier rapidly dissipates from the EVOH copolymer, forming a cohesive, spongy mass that serves to bulk surrounding tissue. Long term results are not available.

The Device consists of two small implantable balloons. During a short procedure, the balloons are surgically placed under the skin next to the bladder. Therapy has been used in more than 1,000 women in Europe, Canada and Australia. It is currently being studied in the United States in a Food and Drug Administration clinical study. Results of a previous study suggest that after a mean follow-up of 36 months, 62% of patients were dry and another 16% were much improved [10]. The use of bulking agents is a good, safe and effective alternative for the treatment of intrinsic sphincter deficiency in male and female patients. Although having lower efficacy than other surgical procedures, represent an alternative minimally invasive approach and may be particularly suited to those who have recurrent urodynamic stress incontinence following previous surgery.

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INJECTION THERAPY: BOTOX IN LUT

Ismail Osman

Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.



Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.

INTRODUCTION

- Botulinum toxin is a **pre-synaptic neuromuscular blocking agent** inducing selective and reversible muscle weakness up to several months, when injected intramuscularly in small doses.
- 1st isolated by van Ermengem in 1897 as the causative toxin producing **clinical Sx of botulism**.
- Clostridium botulinum, a **gram +ve anaerobic bacterium** found in soil, produces 7 immunologically distinct botulinum toxins (BTX) designated A, B, C, D, E, F and G.

2

Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.

PHARMACOLOGY

- BTX-A complex has a size ranging 300-900 kDa (exotoxin + accessory non toxin protective proteins).
- The exotoxin size is 150 kDa, comprises a **50 kDa light chain** and a **100 kDa heavy chain**.
- **BTX heavy chain** allows the toxin to bind to the protein receptor on neural membrane.

3

Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.

PHARMACOLOGY

- Internalization by receptor-mediated endocytosis and separation of chains.
- **BTX light chain** translocates and cleaves a specific protein, responsible for docking, fusion, and release of vesicles containing neurotransmitters into the NMJ.
- Over time **axonal sprouts** form functional synapses that **regress** as the original end plate **re-establishes function**.

4

Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.

CLINICAL PHARMACOLOGY

- BTX-A exert the paralyzing effect by **inhibiting the release of ACh from the motor neuron to the NMJ**.
- **Temporary skeletal muscle** chemodenervation lasts between **3-6 months**, but its clinical effects on the **detrusor smooth muscle** seem to last longer (**6-12 months**).
- Commercially available, BTX-A [Botox®] cleaves the synaptosomal-associated protein of 25-kDa (**SNAP-25**).

5

Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.

CLINICAL PHARMACOLOGY

- With appropriate dosage, BTX-A does not diffuse outside the target muscle, however rare cases of **reversible systemic hyposthenia** for 2-4 weeks were reported.
- **Relative contraindications** to BTX-A treatment are: peripheral motor neuropathy, NMJ disorders (MG, LE syndrome), aminoglycosides and curare-like compounds.
- **Neutralizing antibody formation** is rare with newer BTX-A formulation as the protein content is minimal (5ng/100u).
- Studies demonstrated that **higher doses and shorter intervals** contribute to development of **clinical resistance**.

6



**Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders**

1. Detrusor external sphincter dyssynergia [DESD]
2. Neurogenic detrusor overactivity [NDO]
3. Idiopathic [non-neurogenic] detrusor overactivity [IDO]
4. Obstructive benign prostatic enlargement [BPE]
5. Chronic pelvic pain [CPP]
6. Chronic urinary retention [CUR]

7

**Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.**

1) DETRUSOR SPHINCTER DYSSYNERGIA [DESD]

- Dykstra et al (1988), induced reversible chemo-sphincterotomy with BTX-A in SCI patients with DESD.
- BTX-A injection either **transurethrally** (endoscope), or **transperineally** (EMG control). Both routes had equivalent results [Schurch et al 1996, 1997; Gallien et al 1998].
- 1ry outcomes in most published studies, showed reduction of PVR, MUCP, maximum Pdet and severity of DESD.
- Clinical effects **start after 1 week** and last **up to 6 months**, thereafter re-injection is necessary to maintain efficacy.

8

**Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.**

**1) DETRUSOR SPHINCTER DYSSYNERGIA [DESD]
(cont.)**

- Dose, dilution volume and intervals between 2 injections vary between authors.
- BTX-A (Botox®) 100u, diluted in 4ml normal preservative-free saline injected endoscopically, equidistantly into the 4 quadrants, of the EUS. Clinical effects begin after 1 week and last up to 6 months (Smith et al 2005, Abdelhafeez et al 2005).
- Results are influenced by the detrusor voiding pressure and concomitant internal sphincter dyssynergia.

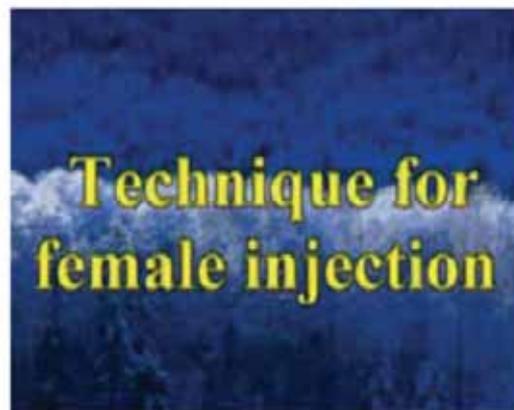
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10



11



INJECTION THERAPY: BOTOX IN LUT (Cont.)

Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.

2) NEUROGENIC DETRUSOR OVERACTIVITY (NDO)

- NDO due to SCI, MMC and MS, causes high intravesical pressure, reduced capacity, low compliance that might lead to UUT damage.
- **Treatment options** rely on: (1) anticholinergic medications with their side effects reducing patient compliance, (2) intravesical vallinoid-antagonists (capsaicin / resiniferatoxin) and (3) CISC.
- **Interventional treatment is irreversible with high morbidity**: sacral nerve stimulation, sacral root rhizotomy, auto-augmentation, enterocystoplasty and ileal conduit.
- **Hypothesis**: Blocking of PS autonomic NS by BTX-A (successful with achalasia / hyperhidrosis).

13

Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.

2) NEUROGENIC DETRUSOR OVERACTIVITY (NDO) (cont.)

- Lab studies demonstrated significant decreases in labelled Ach in BTX-A injected rat bladders after high frequency electric stimulation mimicking up-regulation in cholinergic nerve terminals of SCI bladders.
- **Technique**: each 100u BTX-A is diluted in 10ml preservative free saline or lidocaine. 200 to 300u BTX-A diluted injected in 30 sites equidistantly in the posterior and lateral walls of the bladder, excluding the trigone (avoid VU reflux). Each site receives 10u/ 1ml (Abdelhafeez et al 2005).

14

Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.

2) NEUROGENIC DETRUSOR OVERACTIVITY (NDO) (cont.)

- Schurch et al (2000), demonstrated 6 weeks following injection a significant increase in reflex volume, maximum cystometric bladder capacity, associated with a decrease in maximum detrusor voiding pressure. At 36 weeks FU ongoing improvement occurred.
- The retrospective European multicenter study of 200 cases (Dec 2004) the safety and valuability of the toxin as well as the significant improvement of bladder function and subjective satisfaction in treated patients.

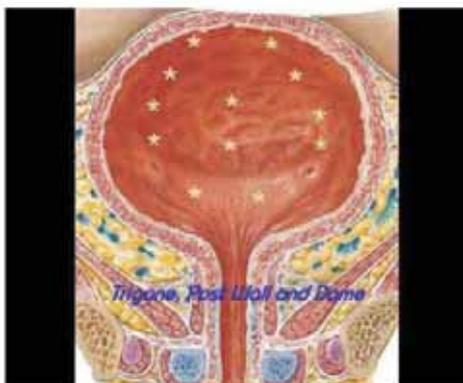
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Botulinum-A Neurotoxin (BTX-A) Applications in Bladder, Prostate and Pelvic Floor Disorders.

3) IDIOPATHIC DETRUSOR OVERACTIVITY (IDO)

- IDO resistant to conservative treatment do benefit from BTX-A injection, showing significant improvement in subjective and objective urodynamics parameters.
- The optimal toxin dose is still yet to be ascertained. 100 and 200u have been used in clinical trials. Elderly subjects should receive lower doses to avoid the risk of retention or significant residual urine (Loch et al 2003, Abdelhafeez et al 2004, Schmid et al 2004).

16



17





19

Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.

4) OBSTRUCTIVE BENIGN PROSTATIC ENLARGEMENT (BPE)

- Obstructive BPE patients, are usually managed successfully medically or surgically.
- While some fail medical treatment, others refuse surgical intervention due to subsequent ejaculatory dysfunction, and others are poor surgical candidates.
- In men, studies following BTX-A injection showed significant improvement of IPSS and flow rate, decreased prostate volume and PSA.

20

Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.

4) OBSTRUCTIVE BENIGN PROSTATIC ENLARGEMENT (BPE)

- Although prostate growth is controlled endocrinally, yet the abundance of adrenergic and muscarinic receptors and nerve fibers suggest an ANS role in growth and secretory function of the gland (Ruggieri et al 1995, Farnsworth 1999).
- A muscarinic receptors subtype was found in BPH and proposed to be responsible for growth stimulation (Ruggieri et al 1995).
- BTX-A blocks these receptors inducing denervation and atrophy of the human prostate.

21

Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.

4) OBSTRUCTIVE BENIGN PROSTATIC ENLARGEMENT (BPE)
(cont.)

- BTX-A injection into the rat prostate induces selective denervation and subsequent generalized atrophy and apoptotic changes in the glandular elements of the prostate (Doggeweller et al 1995).
- Barry et al 1992/1995, demonstrate in a placebo controlled study, randomized 30 patients into 2 groups [15 received BTX -A 200u and 15 received placebo]. At 2 months evaluation, it showed a significant statistical improvement in BTX-A group compared to both placebo group and baseline values.
- Reduction of AUA SxS by 65%*, PSA by 51%*, prostate volume by 68%* and PVR by 83%*. Followup was 19.6 ± 3.8 months.

22

Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.

4) OBSTRUCTIVE BENIGN PROSTATIC ENLARGEMENT (BPE)
(cont.)

- Maria et al 2003, in a placebo controlled study on 30 patients receiving 200u BTX-A into the prostate, reported 65%* improvement in Sx score, a drop 50% in prostate volume and 51% in PSA over 8 weeks compared to placebo.
- Abdelhafeez et al 2005, investigated the effects of injecting transurethral 200u BTX-A, in treating 5 selected cases with refractory obstructive BPO. Follow up after 12 weeks - comparable to baseline - demonstrated reduction in IPSS and improvement in Q parameters, however prostate volume on TRUS did not alter significantly, and serum PSA evaluation was postponed to the 18th week.

23



24

INJECTION THERAPY: BOTOX IN LUT (Cont.)

**Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.**

5) CHRONIC PELVIC PAIN

- Results of different therapies of this syndrome are disappointing.
- Dysfunctional pelvic floor overflows the CNS by a barrage of nociceptive information inducing a change in CNS processing of afferent and efferent informations. BTX-A is supposed to interrupt the afferent branch.

25

**Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.**

**5) CHRONIC PELVIC PAIN
(cont.)**

- Zermann et al (2000), demonstrated significant improvement in chronic prostatic pain following injection of BTX-A 200u transurethrally in perisphincteric area .
- Jarvis et al (2005), demonstrated a decrease in pain and improvement of QOL in 12 females with objective pelvic floor muscle spasm after BTX-A injection into the levator ani muscles (puborectalis / pubococcygeus).
- The GCF retrospective study of BTX-A for treatment of IC, failed to demonstrate any SS objective and subjective outcome at 3 months follow-up.

26

**Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.**

6) CHRONIC URINARY RETENTION

- Reports demonstrated that BTX-A was effective in reducing urethral resistance, facilitating voiding efficiency in patients with dysfunctional voiding.
- Success rates in cauda equine lesion was 62.5%, in idiopathic detrusor underactivity 61.5%, in urethral overactivity 36%, in DESD 27.6%. The mean effect duration was 3-4 months. [Phelan et al (2001) and KUO (2003)].

27

**Botulinum-A Neurotoxin (BTX-A)
Applications in
Bladder, Prostate and Pelvic Floor Disorders.**

CONCLUSION

- BTX-A injections have taken over-times an increasing place in the urologic therapeutic arsenal.
- Mostly indicated in diseases refractory to conservative treatment and before irreversible surgery.
- Large randomized controlled studies are still lacking to prove the efficacy of BTX-A injection on an evidence based medicine level.

Schurch et al. 2004
28



DIAGNOSIS AND MANAGEMENT OF INCONTINENCE IN MEN

Jean-Jacques Wyndaele

1. Types of incontinence to be treated in men

- Post micturition dribble
- Urgency incontinence
- Post prostatectomy stress incontinence
- Mixed incontinence
- Incontinence + poor bladder emptying
- Incontinence + bladder outflow obstruction

2. Special cases

- Complicated incontinence - Recurrent incontinence
- Alarm signs
- + Pain
- + Hematuria
- + Recurrent infection
- + Voiding symptoms
- + Prostate irradiation
- + Radical pelvic surgery
- Neurologic patient
- Frail elderly

3. Levels of management

- Initial management
- Specialized management

4. Evaluation methodology

- a. Levels of evidence (= LE)
 - Depends on trials published
 - Level 1: high level
 - ...
 - ...
 - Level 4: Expert opinion: low level
- b. Grades of recommendation (= GR)
 - Depends on trials published
 - Grade A = highly recommended
 - ...
 - ...
 - Grade D = Evidence inconsistent / inconclusive = no recommendation

Initial management

1. Post micturition dribble

- Manual urethral compression after micturition (= urethral milking)
- LE = 2
- GR = C
- Pelvic floor muscle training > strong contraction PFM immediately postvoid

2. Stress incontinence (sphincteric incompetence)

Post prostatectomy

- Lifestyle interventions GR = B
- Pelvic floor muscle training GR = A
- Bladder training Gr = C
- Continence products
- External appliances

DIAGNOSIS AND MANAGEMENT OF INCONTINENCE IN MEN (Cont.)

1. Lifestyle interventions

- No trials in men
- Smoking
- Obesity
- Sedentary lifestyle
- LE = 4
- GR = D

2. Physical therapy and radical prostatectomy

- Influence of exercises done preoperatively on continence
- LE = 2
- GR = C
- Effect uncertain: can help prepare surgery, give sense of control
- Influence of exercises done preoperatively + postoperatively on continence
- LE = 2
- GR = B
- Modest benefit in early return continence, not over long term
- Exercises for incontinence after TURP
- Reduces length of time incontinence postoperatively but not in long term

3. Acupuncture

- Overactive bladder symptoms
- Incontinence in spinal cord lesion
- Idiopathic detrusor overactivity
- Mixed incontinence
- Effects in men?
- LE = 4
- GR = D
- Mechanism of action?
- Somatic sensory stimulation
- Inhibition spinal-supraspinal reflexes
- Endorphine release
- Protocols?
- Chen YL, Cen J, Hou WG, Gao ZQ, Yu XM, Ma XM Effects of electroacupuncture treatment on nitrergic neurotransmitter in bladder neck and detrusor of rats with unstable bladder. Zhong Xi Yi Jie He Xue Bao. 2006 Jan;4(1):73-5
- the synthesis and secretion of nitrergic neurotransmitter in bladder tissue may be one of the mechanisms of acupuncture in adjusting bladder function.
- Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004462 Thomas et al
- Incontinence after stroke
- Not enough data on acupuncture

3. Incontinence with urgency / frequency

- Urgency incontinence due to detrusor overactivity
- Lifestyle interventions GR= C
- Pelvic floor muscle training GR = C
- Bladder training GR = C
- Bladder relaxant drugs GR = C
- Alfa adrenergic antagonists GR = C



4. Mixed incontinence

Urgency incontinence due to detrusor overactivity + stress incontinence - sphincteric incompetence

- Lifestyle interventions
- Pelvic floor muscle training
- Bladder training
- Bladder relaxant drugs
- Continence appliances

Bladder relaxing drugs

- Antimuscarinics
- Mixed action
- Antidepressants
- Imipramine
- Alfuzosin, Doxazosin, Prazosin, Terazosin, Tamsulosin
- Terbutaline, Salbutamol
- LE = 3
- GR = C

Side effects - Placebo effect

Bladder training

- Bladder training
- Timed voiding
- Habit training
- Prompted voiding
- LE = ?
- GR = C

Specialized management

When basic management has failed

1. Stress incontinence (sphincteric incompetence)

Post prostatectomy

- Artificial urinary sphincter
 - LE = 2
 - GR = B
- Male sling
 - LE = 3
 - GR = C
- Bulking agents
 - LE = 3
 - GR = C

Artificial sphincter for UI after radical prostatectomy

- Artificial sphincter = gold standard
- Long term success 80% or >
- High patient satisfaction 87 – 90 %
- Need periodic revision at 5 years 50%

Male sling(s) for UI after radical prostatectomy

- Not enough studies but recent studies (2006) give success 80% or > in short term
- Most success in minor or mild incontinence

Urethral bulking agents for UI after radical prostatectomy

- Most minimally invasive
- Modest success, low cure rate, effect disappears

DIAGNOSIS AND MANAGEMENT OF INCONTINENCE IN MEN (Cont.)

When to operate for UI after radical prostatectomy

- Conservative 6 – 12 months
 - LE = 4
 - GR = C
- a. Incontinence after prostatectomy for benign disease
 - Same results as for radical prostatectomy
 - Artificial sphincter > male sling > bulking agents
- b. Surgery for incontinence after external beam radiotherapy +/- radical prostatectomy
 - Artificial sphincter though higher complication rate
 - Suprapubic suspension sling less effective
 - Perineal sling more promising
 - Bulking agents : weak results
- c. Incontinence after brachytherapy, cryosurgery,
 - Few data
 - Artificial sphincter promising
- d. Stress urinary incontinence after traumatic injury of the urethra and pelvic floor
 - Artificial sphincter
 - Other treatments sometimes indicated:
 - Stent + artificial sphincter
 - Bladder neck closure + Mitrofanoff
 - Et al

Treatment of complication of artificial sphincter

Diagram exists that follows the different steps starting with controlling of the pumping mechanism

2. Incontinence with urgency / frequency

- a. Refractory urgency incontinence due to detrusor overactivity
 - Neuromodulation
 - Auto augmentation
 - Bladder augmentation
 - Urinary diversion

 - Botulinum –A-toxin injection bladder
 - LE = 3
 - GR = D

 - Electrical stimulation and neuromodulation
 - LE 1-2
 - GR = B
 - but cost !! > limited use

 - Bladder myectomy and augmentation
 - LE = 3
 - GR = C

 - Results 75% - 80%



- b. Detrusor overactivity + bladder outlet obstruction
 - alfa blockers, 5 alfa reductase inhibitors
 - Treatment anatomic bladder outlet obstruction
 - Bladder relaxant drugs
 - Alfa blockers + bladder relaxing drugs
- Detrusor overactivity but detrusor underactive during voiding
 - Intermittent catheterisation
 - Bladder relaxing drugs

3. Mixed incontinence

- Artificial urinary sphincter
- Male sling
- Bulking agents
- Neuromodulation
- Autoaugmentation
- Bladder augmentation
- Urinary diversion

4. Complicated incontinence

- Correct anomaly
- Treat pathology

Take home messages

Look at the diagrams from the ICI 2005 book which will be presented.



MY TAPE IS BEST FOR SUI: TVT – TVT O – TVT SECURE (Gynecare)

Ayman Al Qatawneh

TVT procedure was first described in 1996. It is based on a theory of pathophysiology of stress urinary incontinence. It is the Gold standard with long term demonstrated safety and efficacy. Multiple comparative studies had shown its superiority.

The TVT-Obturator (inside-out) designed to optimize safety and maintain the efficacy; the device is passed away from the bladder and the urethra, minimal dissection allows for accurate and precise midurethral placement.

The new 3d generation TVT-S is still under research, but it looks promising.



MY TAPE IS BEST FOR SUI: SPARC – MONARC (AMS)

Hashim Hashim

What is SPARC?

SPARC™ is a system for delivery and placement of a sutureless, soft-tissue fixation pubourethral retropubic sling for the treatment of female stress urinary incontinence secondary to urethral hypermobility or intrinsic sphincter deficiency.

The name SPARC is derived from the fact that the system is applied using the suprapubic (SP) approach with needles that have an arc (ARC) shape. This approach allows the needles to travel in the zone of safety behind the contour of the suprapubic bone, giving more control over insertion and reducing the risk of damage to major vessels, bowel and bladder although these are major risks of this approach. The needles then exit the vagina in the mid-urethral region.

The sling used is a polypropylene mesh, which facilitates tissue in-growth for rapid sling fixation without suturing. It has a tensioning suture which allows for intra-operative refinements and even sling adjustment in the postoperative period. The 3.0mm wide and 22cm long needles are slender with a blunt tip, thus causing less tissue trauma.

Procedure

- Make one vaginal and two suprapubic incisions. No introducer or catheter guide is required.
- Pass the needles down the posterior side of the pubic bone – angle it slightly so that the needle tip penetrates the endopelvic fascia approximately 2cm lateral to the urethra. The needle tip stays in contact with pubic bone until endopelvic fascia is penetrated.
- Insert the index finger through the vaginal incision to meet the tip of the needle and guide it through the incision.
- Repeat the above procedure with the other needle through the other incision.
- When both needles are in place, cystoscopy is performed (only one cystoscopy is required) to check that the bladder is not perforated.
- The sling is not pre-attached to the needles, to allow ease of needle manipulation) and you should attach it when the needles pass through the vaginal incision using the supplied sling-connectors.
- Pull the sling through the suprapubic incisions with the needles and place it in a sub-urethral position without tension.
- You can now remove the plastic sling cover and adjust the tension on the sling and trim the mesh to the required size.



MY TAPE IS BEST FOR SUI: SPARC – MONARC (AMS) (Cont.)

What is MONARC?

The Monarc™ Subfascial Hammock has a hammock-shaped mesh with lateral fixation that aims to mimic and restore the normal anatomical pubourethral ligament support based on DeLancey's Hammock theory.

It utilizes the trans-obturator route which has the advantage of avoiding the retropubic space and thus damage to bowel and bladder with less reliance on cytoscopy. However there is the risk of damage to the obturator artery (traverses the obturator canal at the anterolateral upper margin of the obturator foramen) and nerve.

The mesh is 35cm long, 4-0 woven, open weave, monofilament, polypropylene with a resorbable tension suture, for post-op adjustment. It has a protective plastic sheath and a locking needle-to-mesh connector system for extra security.

The needles are helical in shape to facilitate their safe passage from skin to vagina (outside-to-in) around the ischiopubic ramus, passing away from the vessels rather than towards them. The needles are 3mm in diameter to reduce tissue disruption and have a blunt tip for safe fingertip feeling. There is about 1-2cm blind needle passage during the procedure and the needle path is about 3-4cm away from the obturator artery.

Procedure

- The procedure can be done under local, regional or general anesthesia.
- Catheterise the patient.
- Make a 1.5cm – 2cm incision along the anterior vaginal mucosa, 0.5 cm distal to the urethral meatus.
- Dissect the vaginal epithelium, bilaterally, off the underlying periurethral fascia, to the inferior pubic ramus.
- Identify the internal edge of obturator foramen from the outside.
- Introduce index fingertip and palpate the obturator canal.
- Make a skin incision in or just medial to the genito-femoral fold at the base of the adductor longus tendon, approximately at the level of the clitoris.
- Use forceps to open and expose the vaginal tunnel to facilitate passage of the connector and mesh later on.
- Insert the needle along the medial edge of the ischiopubic ramus just below the insertion of the adductor longus tendon at approximately the level of the clitoris.
- The needle will perforate:
 - 1) obturator externus muscle
 - 2) obturator membrane
 - 3) obturator internus muscle
 - 4) periurethral endopelvic fascia and
 - 5) exits through the vaginal incision
- Attach the mesh and retract the needle along same path as insertion keeping the needle shaft parallel to the descending ramus, at 45 degree angle to the patient's midline and close to the patient's body. The tape should sit medial and inferior to the muscle insertion.
- You can use the opposite hand on the outside of the needle curve to assist reverse rotation and mesh passage.
- Leave a small space (3mm – 5mm) between urethra and mesh.
- Close the vaginal and skin incisions with 3/0 undyed synthetic absorbable sutures.
- Remove the catheter.





MY TAPE IS BEST FOR SUI: ARIS (Coloplast)

Hassan Shaker

The introduction of the TVT followed by the TOT techniques for placement of suburethral tapes has revolutionized the treatment of SUI and set new treatment standard. The advantage of the polypropylene became clear over other synthetic materials and 10s of tapes have been introduced to treat this condition.

The distinction between these tapes should be ideally addressed through head to head comparison regarding the results and complications. Unfortunately, very few randomized comparative trials are present serving this purpose. For that reason, the advantages of ARIS over other tapes can be addressed through several points. The theoretical advantages of the tape material, the outstanding results of the tape, and the advantage of the technique used for tape insertion are in my opinion can solve this dilemma.

As regards the material, it is a knitted macroporous monofilament polypropylene. The monofilament feature of the polypropylene has demonstrated its superiority over the multifilament form for a long time in the surgical suture material as bacteria can insinuate themselves between the multifilaments. By the same token, macroporous property is mandatory for the macrophages to get into these pores combating infection. Furthermore, it allows the in-growth of body tissue into the pores incorporating the tape within these tissues. The larger the pores the better it is. ARIS has the largest pores in the market. Being knitted is another advantage that has been appreciated after the high complication rate in the non-knitted thermally linked tapes.¹ The density of the material reflects the weight of the foreign material to be left in the body. Again ARIS has the one of the lowest densities among different tapes in the market. The procedure used for suburethral placement of ARIS is the one developed by Delrome "the outside in transobturator technique". This surgery has proved its simplicity with easy learning curve, and low complication and high success rates.² Head to head comparison with TVT have shown that it is equally efficacious but with lower morbidity and complications.³ There is as well a theoretical advantage of this method when compared to the inside out TOT as shown in cadaveric dissections subjected to both procedures being safer on the obturator bundle.⁴

The largest database available regarding the outcome of the ARIS is the one of the European registry. This is a multicentre study. It involved 368 patients until this moment. Short term results have shown outstanding cure rate of 87% and improvement of 8.5%. For patients that have been followed up for more than one year, the cure rate was 91% and improvement of 5.7%. Complications were minor in about 10.6% of patients and included bleeding (1.4%), Bladder perforation (0.8%), Urethral perforation (0.5%), post operative long term retention (0.5%) necessitating cutting the tape, haematoma (0.8%) and vaginal erosion (0.8%). (Personal Communication)

Although ARIS is the most recently introduced tape, its design was based on past experience of success and failures of other older tape. The material design, technique, and short term results assure that this tape is the best for treatment of SUI.

¹ Siegel A. Vaginal mesh extrusion associated with use of mentor transobturator sling. *Urology* 66: 995-999, 2005.

² Delorme E: Transobturator urethral suspension: miniinvasive procedure in the treatment of urinary stress incontinence in women. *Prog Urol* 11: 1306-1313, 2001.

³ Fischer A, Fink T, Zachmann S, Eickenbusch U: Comparison of Retropubic and Outside-In Transobturator Sling Systems for the Cure of Female Genuine Stress Urinary Incontinence. *European Urology* 48: 799-804, 2005.

⁴ Delmas V: Anatomical risks of transobturator suburethral tape in the treatment of female stress urinary incontinence. *Eur Urol.* 48(5): 793-8, 2005.

MY TAPE IS BEST FOR SUI: URETEX (Bard)

Waleed Al Taweel

The development of suburethral and other pelvic slings with tension free surgical principles developed by Petros and Ulmsten has led to surgeons becoming more comfortable with the concept of restoring the anatomy by tape or mesh placement in the vagina.

Stress incontinence and prolapse have proven to be difficult clinical problems to solve. Patient expectations have increased in parallel with the improved quality of life available for women around the world.

The last 20 years have seen an explosion in the number of procedures and techniques available as clinicians attempt to meet these expectations. Mesh related problems might be attributed to the characteristics of the mesh, errors in technique, poor tissues and haematoma. Mesh characteristics, which influence the behaviour of prosthesis, include the type of polymer, the weight, density and thickness of polymer, the pore size, the size of the contact surface of the mesh, the structure of the mesh (monofilament or multifilament) and the specific configuration or weave of the mesh.

Low-density meshes have been shown to be associated with less scarring and tissue shrinkage, better biocompatibility and reduced mesh extrusion. It has been shown that Uretex is one of the best meshes with strong, stable, retain memory, shape and no reported cases of erosion. On top of that, previous studies confirmed its cure rate and improvement of patient symptoms, quality of life and sexuality.



