Minimally invasive treatment for female stress urinary incontinence – Romanian highlights

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Abstract
Rationale: Stress urinary incontinence is still a "battlefield" for many minimally invasive therapies, but, unfortunately, few can restore the anatomical and functional background of this disorder.
Objective: Assessing the latest minimally invasive procedures of intra and perisphincterian injection of autologous stem cells.
Method and Result: The first stem cell implantation (myoblasts and/or mature fibroblasts grown and multiplied in the laboratory from biopsy samples taken from the pectoralis muscle) in the urethral sphincter was performed on October 18, 2010, in “Fundeni” Clinic of Urology and Renal Transplantation, in Romania.
Discussion: The follow-up at six weeks with the quality of life questionnaires, micturition diary and clinical examination revealed a decrease of urine loss from six pads/day at one per day, which significantly improved the patient’s quality of life according to visual analogue scale. Clinical and urodynamic evaluations will continue and will be future scientific topics.

Key Words: stem cells; myoblasts; transplantation; urethral sphincter

Abbreviations: SUI = stress urinary incontinence; TVT = tension free vaginal tape; TVT-O = tension free vaginal tape obturator; QoL = quality of life

Introduction
Although not life threatening, stress urinary incontinence (SUI) is certainly a public health problem, affecting the quality of life, mainly of the female population. It is a symptom/sign/condition defined by involuntary loss of urine that occurs during physical activity, with the effort of coughing, sneezing, laughing, prolonged standing, sexual activity etc. [1] Its prevalence reaches alarming rates, about 20% of total female population being affected; percentages increasing to 35% for those aged over 60 years [2,3].

The most important risk factors for SUI are: female sex, childbirth, obstetric history, lifestyle, chronic cough (chronic bronchitis, asthma), advanced age, estrogen status, obesity and history of pelvic surgery [4-8].

The normal functioning of the lower urinary tract and that of the nervous system assures the urinary continence and the act of micturition. Two different muscular structures are mainly involved in controlling the act of micturition: the urethral sphincter, which controls continence and facilitates micturition and the bladder muscle layer, the detrusor, which has the unique properties of gradually distending to allow the filling of the bladder, with minimal pressure increase, followed by efficient contraction in order to void.

Various conditions lead to pelvic floor structures dysfunctions, and so the base of the bladder and the urethra weaken, with urinary incontinence during increased abdominal pressure (coughing, laughing, sneezing, exercise).

Still, it has been described as a pathological entity in which the components of the pelvic floor are not affected and still the urine loss persists, the mechanism being described as intrinsic sphincter deficiency [1].

The management of SUI is not easy, as therapeutic approach varies from conservative methods including lifestyle changes, medication, pelvic floor muscles exercises, electro stimulation, to minimally invasive - injection of collagen, suburethral slings reserving invasive surgical treatment for complex, recurrent cases [9].
Method

The anatomical and functional restoration of the pelvic structures is a challenge for many minimally invasive therapies, and just a few have succeeded. Intrinsic urethral sphincter deficiency and abnormal mobility of the urethra emerged as a key mechanism underlying the occurrence of this condition, along with other pathogenic theories. More recently, according to the “trampoline” theory, any structural defect in the pelvic ligaments, bones, fascial structures may contribute to the impairment of the pelvic muscle cybernetic system. However, clinical experience has shown that not all lesions have a proportional role in the development of SUI and the mechanism of urethral sealing - mainly muscular, contributes fundamentally to the achievement of urinary continence. It is not a lower density of skeletal muscle fibers in the urethral sphincter structure, involved in the appearance of SUI? Although there are controversies in the literature, many studies showed a reduction in muscle fibers density in a category of patients from which we have excluded all other pelvic pathologies. Thus, theoretically an artificial increase of the number of muscle fibers in the structure of the urethral sphincter could represent an innovative solution. Among the latest minimally invasive procedures, the injection of autologous stem cell intra and around the intrinsic sphincter is one of the most anatomical and functional methods, as seen in Figure 1 (myoblasts and/or mature fibroblasts multiplied in the laboratory from biopsy samples taken from the pectoral muscles). This method has proven clearly superior to the injection of collagen, it is not associated with major side effects, has minimal morbidity rates, reduced mean hospitalization time and although still experimental, it stands to be a promising procedure in the near future. The use of stem cells (myoblasts) as implants is a paradigm shift of the current treatment for SUI, currently based upon using synthetic materials (such as polypropylene mesh), that although well tolerated, they can never replace the auto/allograft in terms of biocompatibility. In addition, the anatomical restoration of the defects means a return to the "restitutio ad integrum" principle and not just a simple adjustment in order to resolve a pelvic static problem.

With over 30 years of clinical experience in renal transplantation performed in “Fundeni” Clinic of Urology and Renal Transplantation, with pioneers of urodynamic studies and surgical treatment of pelvic static disorders in Romania working in this Center, our specialists have actively participated in the clinical research of female pelvic disorders. In addition, the expertise gained in the most important Renal Transplantation Center from Central and Eastern Europe – the “Fundeni” allows and provides the infrastructure needed for the development of this project.

For every study regarding SUI, selecting patients with stress urinary incontinence mainly caused by urethral sphincter deficiency is a difficult task.

Medical history, physical examination in conjunction with urodynamic studies are the necessary steps to recruit patients in the study group, which later will be compared to a control group to whom a standard minimally invasive procedure is performed according to the guidelines of the Romanian Association of Urology, European Association of Urology and International Society of Continence. Many variables, such as age, performance and estrogen status, medical and surgical history, the severity of SUI, previous therapies both medical and surgical performed for the treatment of pelvic disorders, have to be taken into account to create well balanced study groups. Based on clinical evidence and on the results obtained from patient’s follow-up, randomized, multicenter, well-managed studies will be designed in the future. Stem cell implantation in the urethral sphincter was performed for the first time in Romania on October 18, 2010, in “Fundeni” Clinic of Urology and Renal Transplantation. The team was led by Professor Dr. Ioan Sinescu and was made up of Dr. Cristian Surcel, Dr. Alexandru Iordache, Dr. Calin Chibelean, Dr. Cristian Mirvald, Dr. Carmen Savu, Nurse Liviu Andrei and Professor Rainer Marksteiner. Standard protocol was applied without incidents, the patient being discharged after 24 hours. The follow up at six weeks revealed a stunning improvement in the patient’s quality of life (QoL) and continence rate, certified by clinical examination, QoL questionnaires and frequency-volume chart. The leak was reduced from six to one pad/day. Clinical and urodynamic follow up continues and will be a future scientific topic.

From a technical standpoint, the procedure involves four major stages:

1. Selecting patients with SUI with intrinsic sphincter insufficiency.
2. The collection myoblasts from the pectoris major muscle, a maneuver easy to perform, with a short learning curve.
3. Isolation of stem cells (myoblasts) and multiplying them in cell cultures at the Center of Excellence in Cell and Tissue Research in Innsbruck, Austria. (Figures 2 and 3)
4. The surgical procedure of stem cells implantation in the urethral sphincter.

It requires a special biopsy device – Sonoject - which includes a central piece through which the biopsy is being performed, that provides an adapter to a syringe containing the cell suspension and a channel for a 20 MHz circular ultrasound probe that is used to locate the external urethral sphincter and to guide the injections. The device is fixed to a metal arm that is attached to the surgical table (similar to that used in prostate brachytherapy) together with a metal cylinder that slides manually, on which the “Sonoject” is locked on.

The procedure takes place with the patient in lithotomy position, under general anesthesia. The pubic region, internal thighs and perineal area are sterile draped. Before the procedure, the device is assembled and tested in a saline solution or sterile water. Thus the circular ultrasound probe is calibrated in order to detect the needle and its signal.

The bladder is filled with 200 mL of saline and the device is inserted through the urethra. The system is armed so it does not move during the maneuver and the surgeon identifies the bladder neck, urethra and urethral sphincter (Figure 4). Once established the injection site, the cell suspension solution is injected on the anterior side of the sphincter, in two different semi-circular quadrants. The procedure needs 20 different injection sites, with 100 µL of solution. At the end of the procedure, the device is withdrawn from the urethra and disassembled.

Discussion

At least three surgical specialties treat pelvic floor pathology. Posterior compartment prolapse and anal incontinence are evaluated by the general surgeon or proctologist, uterine and vaginal prolapse, dyspareunia by the gynecologist and cystocele and low urinary tract symptoms by the urologist. Urinary incontinence and pelvic floor prolapse are two pathological entities that gave birth to the fourth specialist: the urogynecologist. The pathogenesis of SUI is multifactorial and so, the management is difficult, requiring clinical and therapeutic experience and for this reason many patients receive an incomplete treatment, which often worsens the clinical background or trigger symptoms caused by other structures which at the time of presentation were compensated.

Suburethral slings, inserted transobturatory, were introduced in Europe several years ago. This procedure was carried out by urogynecologist despite the absence of long-term data regarding efficiency and the rate of healing. The same approach happened with TVT (tension free vaginal tape) when they were introduced and, although the medium and long term data were lacking, they were adopted and became today’s gold-standard treatment for SUI in women.

According to Abdel-Fattah’s recently published series of reports [14,15] that assessed the preferences for
minimally invasive treatment of SUI, one third of responders considered that TVT-O (tension free vaginal tape obturator) is an up-to-date procedure and it must be immediately applied, while the others expect the medium and long term statistics. Thus, stem-cell- myoblasts therapy may represent an alternative in the future, everyday intervention, in the urologist’s armamentarium. At least for the group of patients, to whom, from the pathogenic point of view, the deficiency is limited to the urethral sphincter, we believe that the urologist’s interest should be maximal. The effectiveness of this treatment can change the course of therapy and last but not least, the accessibility to urological evaluation of patients with SUI.

Treatment is tailored to the patient’s suffering and not just treats the leak of urine. In other words, a successful therapy includes the main objective parameters (dry/wet) and the subjective quality of life which is assessed by questionnaires [16]. However, understanding the “results” and the statistical methods used in their quantification are not homogeneous and sufficiently clear in order to remove any controversy. Before we compare and decide which the most effective procedure is, we should reach a consensus regarding the definition of “results”, how they should be measured, follow-up intervals, etc. Until these issues are clarified, the urologist will continue to choose one of the many existing procedures and will remain autonomous in his selection. Thus, the need for new therapeutic methods, that can restore the integrity of the pelvic structures as close as possible, is urgent. The Centers of Excellence in Urology must develop research programs and be partners in multicenter studies in order to obtain solid long term data. Thus, new standards will be created that will be approved by urologist everywhere.

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