Highlights in the minimally invasive treatment of SUI in women

Surcel C*, Chibelean C*, Iordache A*, Mirvald C*, Gingu C*, Margaritis S*, Stoica R*, Codoiu C*, Savu C*, Marksteiner R**, Sinescu I*

*"Fundeni" Clinic of Urology and Renal Transplantation, Bucharest, Romania
**Life Science Center Biotechnologie Innsbruck, Austria.

Correspondence to: Assist.Prof. C. Surcel, MD, PhD
"Fundeni" Clinic of Urology and Renal Transplantation, Bucharest, Romania
Telephone: +40 744 963 035
Email: drsurcel@gmail.com

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Abstract

Objective: Treatment of stress urinary incontinence consists of a wide range of options, from conservative therapies like lifestyle changes, medication, pelvic floor muscles exercises, electro-stimulation, to minimally invasive procedures- injection of collagen, suburethral slings TVT / TOT and last but not least, invasive surgical treatment reserved for recurrent and complex cases. Among the latest minimally invasive procedures reported in literature, the injection of intra-and perisphincterian of autologous stem cell (mioblasts and /or mature fibroblasts grown and multiplied in the laboratory from biopsy samples taken from the pectoralis muscles).

Material and method: On October 18, 2010, in “Fundeni” Clinical Institute of Uronephrology and Renal Transplantation was performed the first stem cell implantation procedure in the urethral sphincter, in Romania.

Results: Assessment at 6 weeks, the quality of life questionnaires, micturition diary and clinical examination revealed a stunning decrease of urine loss from 6 pads / day at one per day, which significantly improved the patient's quality of life.

Conclusions: Stem-cell- mioblasts therapy may represent in the future an every-day intervention in the urologist's armamentarium. The effectiveness of this treatment can change the course of therapy and last but not least, the accessibility to urological evaluation of patients with stress urinary incontinence. Clinical and urodynamic evaluations will continue and will be future scientific topics.

Key words: stress urinary incontinence, stem cells, urethral sphincter, minimal invasive treatment.

Introduction

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

Urinary continence and the act of micturition depend on the normal functioning of the lower urinary tract and of the nervous system. Two muscular structures are mainly involved in controlling the act of micturition:
- the urethral sphincter, which must be fully functional in order to facilitate continence and micturition;
- the detrusor, the bladder muscle layer, which should gradually relax to allow the filling of the bladder and to contract efficiently in order to eliminate the urine.

Whenever the pelvic floor structures are impaired, the base of the bladder and the urethra would weaken, with the appearance of urinary incontinence due to the increasing of the abdominal pressure during efforts (coughing, laughing, sneezing, exercise). In addition, it has been described an entity in which the components of the pelvic floor are not affected, still the urine loss persists, the mechanism being described as intrinsic sphincter deficiency [1].

Among the most important risk factors reported in the occurrence of stress urinary incontinence (SUI) are mentioned: female sex, multiparity, obstetric history, lifestyle, chronic cough (chronic bronchitis, asthma), advanced age, estrogen status, obesity and history of pelvic surgery [4, 5, 6, 7, 8].

The treatment of SUI consists in a wide range of options, from conservative therapies including lifestyle changes, medication, pelvic floor muscles exercises, electrostimulation to minimally invasive - injection of
collagen, suburethral slings TVT/TOT and invasive surgical treatment reserved for complex, recurrent cases [9].

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. Intrinsc urethral sphincter deficiency emerged as a key mechanism underlying the occurrence of this disease, along with other pathogenic theories, such as hipermobility of the urethra. Moreover, 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 [10]. 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 structure of the urethral sphincter involved in the appearance of SUI? The literature is contradictory, but many studies show a reduction in muscle fibers density in a category of patients from which we had excluded all other pelvic pathology [11, 12]. Thus, theoretically an augmentation of the number of muscle fibers in the structure of the urethral sphincter could represent an innovative solution.

Material and method

Among the latest minimally invasive procedures includes the injection of autologous stem cell intra and around the intrinsic sphincter as seen in Figure 1 (mioblasts 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, not being associated with major side effects, with minimal morbidity, reduced mean hospitalization time and even if it is still in an experimental stage, it stands to be a promising procedure in the near future. Given the significant clinical experience in renal transplantation activity performed in “Fundeni” Clinic of Urology and Renal Transplantation of over 30 years, coupled with the urogynecologic expertise made by the pioneers of urodynamic evaluation and surgical treatment of pelvic static disorders in Romania, our Center actively participates 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” Clinic allows and provides the infrastructure needed for the development of this project.

In fact, selecting those patients with stress urinary incontinence, in which the main pathogenic mechanism is represented by urethral sphincter deficiency, is not an easy task.

Urodynamic evaluation in conjunction with physical examination and medical history are the necessary steps in gathering the patients included in the study group which later, in time, will be compared to a control group to whom a standard minimally invasive is performed according to the guidelines of the Romanian Association of Urology-European Association of Urology and International Society of Continence. Finding well balanced groups regarding 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, are becoming reasons for concern to bring into daily practice such procedures in the future. Based on the clinical evidence and the results obtained from follow-up, randomized, multicenter, well-managed studies, SUI will be designed. The implantation of stem cells (mioblasts) implies a paradigm shift in the current treatment of SUI which is currently using synthetic materials such as polypropylene which, although well tolerated, they can never replace the auto/allografts in terms of biomaterials quality, and organic compatibility. In addition, the anatomical restoration of the defects mean a return to the “restitutio ad integrum” principle and not just a simple adjustment in order to resolve a pelvic static problem.

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

1. Selecting patients with SUI with intrinsic sphincter insufficiency.
2. The collection of biopsy material (mioblasts) from the pectoris major muscle. It is a maneuver easy to perform, with a short learning curve.
3. Isolation of stem cells (mioblasts) and multiplying them in cell cultures at the Center of Excellence in Cell and Tissue Research in Innsbruck, Austria. (Figures 2 and 3)
saline solution or sterile water. Thus we can calibrate the circular ultrasound in order to detect the needle and its signal.

Afterwards, we put the device in the bladder after it has been previously filled with 200 cc of saline. The system is armed so it does not move during the maneuver in order to identify the bladder neck, urethra and urethral sphincter (Figure 4). Once established the injection site, we introduce the cell suspension solution on the anterior side of the sphincter, in two different semi-circular quadrants. The maneuver stops after we punctured in 20 different sites with 100 µL of solution. At the end of the procedure, the device is withdrawn from the urethra and disassembled.

4. The surgical maneuver of stem cells implantation in the urethral sphincter

It involves the use of a special biopsy device - Sonoject- which contains 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 20MHz circular ultrasound arm 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 brachytherapy) together with a metal cylinder that slides manually, on which the "Sonoject " is locked on.

The patient is placed in lithotomy position under general anesthesia. The pubic region, internal thighs and perineal area are disinfected and draped properly. Before the procedure, the device is assembled and tested in a

On October 18th 2010, in “Fundeni” Clinic of Urology and Renal Transplantation was performed the first stem cell implantation procedure in the urethral sphincter in Romania. The team was led by Professor Dr. Ioan Sinescu and was made out of Dr. Cristian Surcel, Dr. Alexandru Iordache, Dr. Calin Chibelean, Dr. Cristian Mirvald, Dr. Carmen Savu, Nurse Liviu Andrei and Professor Rainer Marksteiner. The procedure followed the standard protocol without incidents, the patient being discharged after 24 hours.

**Results**

Assessment at 6 weeks, containing a clinical examination, QoL questionnaires and voiding diaries, revealed a stunning improvement, the loss of urine being reduced from 6 pads/day to one per day, with a significantly improvement in the patients’ quality of life. Clinical and urodynamic evaluations will continue, being the topics of future scientific research.

**Discussions**

The pelvic floor contains structures whose pathology is treated by at least three surgical specialties.
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 occur as a result of structural damage to several components of the urogenital diaphragm. Thus, according to the first symptoms that appear, the first presentation to the doctor, the outcome of treatment, follow-up are carried out by the specialist who treated only a symptom for which the patient initially presented, though as we mentioned above, the pathogenesis is multifactorial and the symptoms appear after the breakdown of the structures with a high grade of fragility. For this reason, many patients receive an incomplete treatment, which often worsens the clinical background or trigger other 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 thing happened with TVT’s 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. Abdel-Fattah has recently published a series of reports [14, 15] that assessed physicians’ preferences for minimally invasive treatment of stress urinary incontinence. The results were encouraging and emphasized that one third of respondents considered that TVT-O was a procedure up-to-date and must be applied immediately, while others expect the medium and long term statistics.

Treatment is tailored to the patient’s suffering and not just treats the loss 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 is the most effective procedure, we should reach a consensus on 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 procedure and will remain autonomous in his selection. Thus, the need for new therapeutic methods, that can restore as close as possible the integrity of the pelvic structures, is urgently required.

Conclusions

Stem-cell- mioblasts therapy may represent in the future an everyday intervention in the urologist’s armamentarium. At least for this group of patients, to whom, from the pathogenic point of view, the deficiency is limited to the urethral sphincter, part of the excretory system, 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 stress urinary incontinence.

The Centers of Excellence in Urology must develop research programs and become partners in multicenter studies in order to obtain solid long term data. Thus, new standards will be created that will be approved by urologists everywhere.

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