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Comparative analysis of different surgical procedures for female stress urinary incontinence. Is stem cell implantation the future?

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Abstract

Rationale: Stress urinary incontinence (SUI) represents a major public health problem and although there are many treatments available, only a few can restore the anatomical background of this disorder. Injections of stem cells into the middle urethra have the possibility of restoring the contractility of the striated muscles and rhabdosphincters. The aim of stem cell therapy is to replace, repair or enhance the biological function of damaged tissue or organs. *Objective*: Assessing the latest minimally invasive procedures of intra and perisphincterian injection of autologous stem cells and to compare the urodynamic results at one year after different surgical procedures for genuine stress urinary incontinence by measuring their impact on urinary flow rate (Qmax) and bladder pressure at Qmax during micturition. *Methods and Results*: On October 18, 2010, in "Fundeni" Clinic of Urology and Renal Transplantation we performed for the first time in Romania, stem cell implantation in the urethral sphincter in four patients with stress urinary incontinence and compared the results of the urodynamic investigations of female patients operated with pure SUI with other surgical techniques. The analyzed procedures were: Burch colposuspension (11 cases), TVT-like (IVS sling in 26 cases), TOT-like (CYSTO-SWING sling in 41 cases). Followed variables were: Qmax, Pves at Qmax, postvoiding residual (PVR). Clinical examination and voiding diary in six weeks after the surgery revealed a decrease of urine loss with an improvement of the patient's quality of life according to visual analogue scale. For female patients with myoblasts implant, changes in Qmax and Pves at Qmax were minimal and statistically insignificant in the context of inclusion criteria, but we noticed a trend of minimal change in these urodynamic characteristics, namely, an average decrease of Qmax with 2.1 mL/s and an average increase of Pves at Qmax with 0.6 cmH_2O. *Conclusions*: The development of myoblasts implant (if they will pass the time-proof test) could represent a breakthrough in treating this condition. As the pathogenesis of SUI is better understood and the development of tissue engineering technology advances, tissue engineering will play a more important role in the treatment of patients with SUI.

Keywords: stem cells, myoblasts, urodynamic, stress urinary incontinence.

Abbreviations: SUI – stress urinary incontinence, TVT – tension free vaginal tape, TVT-O – tension free vaginal tape obturator, QoL – quality of life, MDSC – muscle-derived stem cells.

Introduction

Stress urinary incontinence (SUI) represents a public health problem, and although not life threatening, it affects the quality of life, especially of the female population. SUI is defined by loss of urine that occurs involuntary during physical activity, coughing, laughing, sneezing, sexual activity, prolonged standing, etc. [1]. The prevalence rated is about 20% of total female population, percentages increasing to 35% for patients over 60 years [2, 3].

The risk factors for SUI are obstetric history, childbirth, chronic cough (asthma, chronic bronchitis), obesity, advanced age, history of pelvic surgery [4–8].

Normal statuses of the lower urinary tract and of the nervous system are mandatory in order to maintain the urinary continence and the act of micturition. The muscular structures involved in controlling micturition are: the urethral sphincter and the detrusor, the bladder muscle layer which gradually distending to allow the filling of the bladder with minimal pressure increase followed by normal contraction in order to void.

Many conditions lead to pelvic floor structures dysfunctions with urinary incontinence during events that increase the abdominal pressure (laughing, coughing, prolonged standing, sneezing). The involuntary loss of urine but with normal pelvic floor components of appears in a pathological entity with the mechanism described as intrinsic sphincter deficiency [1].

The management of SUI is complex as therapeutic approach varies from methods including medication, pelvic floor muscles exercises, electro-stimulation and life style changes to minimal invasive – suburethral slings, injection of collagen and an invasive surgical approach for recurrent cases [9].

Anatomical and functional restoration of the pelvic structures is a goal for many minimally invasive therapies and just a few have succeeded. The deficiency of intrinsic urethral sphincter and an abnormal mobility of the urethra are the mechanisms underlying the occurrence of this

condition, along with other pathologic theories. Recently, according to the "trampoline" theory, any defect in the structure of pelvic bones, ligaments, fascias may contribute to the impairment of the pelvic floor. The most anatomical and functional method of minimally invasive procedures is the injection of autologous stem cell intra and around the intrinsic sphincter, as seen in Figure 1 (myoblasts and/or mature fibroblasts multiplied in the laboratory from biopsy samples taken from the pectoral muscles).

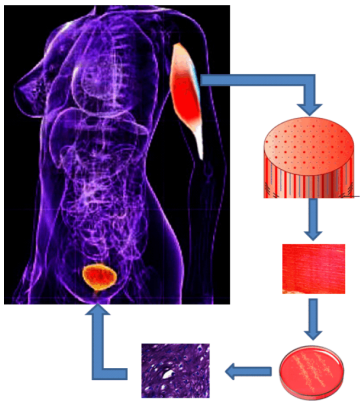

Figure 1 – ***Theoretical scheme of stem cells implantation.***

Compared to the injection of collagen, this method has proven clearly superior, it is not associated with major side effects with reduced mean hospitalization time, minimal morbidity and the use of stem cells (myoblasts) as implants stands to be a promising procedure in the near future in the current treatment for SUI. The methods using synthetic materials, such as polypropylene mesh, although well tolerated, can never replace the auto/allograft in terms of biocompatibility.

The anatomical restoration of the defects of the pelvic static problem is a return to the "*restitutio ad integrum*" principle and not just a simple method of therapy.

Patients and Methods

On October 18, 2010, in "Fundeni" Clinic of Urology and Renal Transplantation, we performed for the first time in Romania, stem cell implantation in the urethral sphincter in eight patients with stress urinary incontinence and we compared the results of the urodynamic investigations at one year of female patients operated with genuine SUI with different surgical techniques. The analyzed procedures were: Burch colposuspension (11 cases), TVT-like (IVS sling in 26 cases), TOT-like (CYSTO-SWING sling in 41 cases) and myoblast implant (eight cases). Followed variables were: Qmax, Pves at Qmax, postvoiding residual (PVR) and impact on QoL.

From a technical point of view, the procedure involves four major stages:

1. Selecting patients with involuntary loss of urine and intrinsic sphincter insufficiency.
2. Collection of myoblasts from the pectoral muscles.
3. Isolation of stem cells and multiplying them in cell cultures at the Center of excellence in Cell and Tissues Research in Innsbruck, Austria (Figures 2 and 3).
4. Implantating the stem cells in the urethral sphincter.

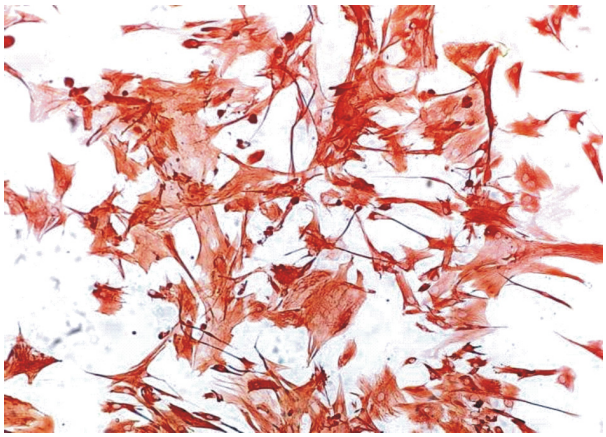

Figure 2 – ***Myoblast growth in cell culture, anti-desmin staining, 200× (with permission from Prof. Marksteiner).***

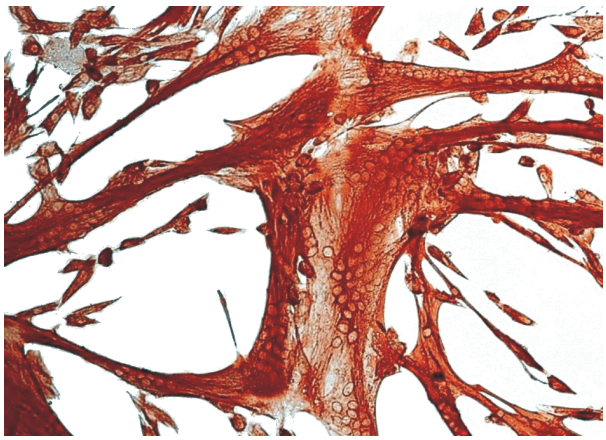

Figure 3 – ***Myoblasts fusion to the myotubuli in cell culture, anti-desmin staining, 200× (with permission from Prof. Marksteiner).***

The surgical procedure requires a special biopsy device, "Sonoject" with a central piece through which a biopsy is being performed that provides and adapter to a syringe with the cell suspension and a channel for the ultrasound probe used to guide the injections and to locate the external urethral sphincter. This device is attached to a metal arm that is fixed to the surgical table together with a metal cylinder that slides manually, on which the "Sonoject" is locked. This method needs 20 injections sites with 100 µL of solution. The device is withdrawn from the urethra and disassembled at the end of the procedure (Figure 4).

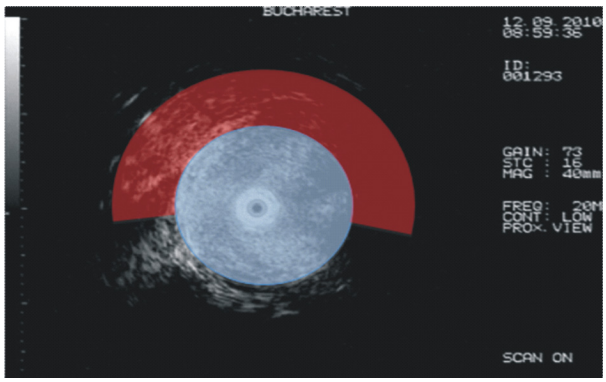

Figure 4 – ***Urethral sphincter ultrasound: intra-operative aspect.***

Average age was 54.9 years (46–78 years) and all patients were surgically naïve for SUI condition.

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 per day at one per day, which significantly improved the patient's quality of life according to visual analogue scale.

In terms of urodynamic findings, at one year after surgical procedures for stress urinary incontinence, we observed that a decrease of Qmax and an increase of Pves at Qmax are more frequent after Burch colposuspension (7.7 mL/s and 8.6 cmH_2O), and less for TVT and TOT. Otherwise, we observed only an adjustment of Qmax and Pves values according to the anatomical principle of the anti-incontinence procedure – the creation of BOO, most of them being, unfortunately, non-physiological.

For female patients with myoblasts implant, changes in Qmax and Pves at Qmax were minimal and statistically insignificant in the context of inclusion criteria, but we noticed a trend of minimal change in these urodynamic characteristics, namely, an average decrease of Qmax with 2.1 mL. Significant changes in urinary flow were observed for all surgical procedures, except for myoblast injection. Urethral profilometry data obtained were inconsistent with the standard urodynamic evaluation protocol (Figure 5).

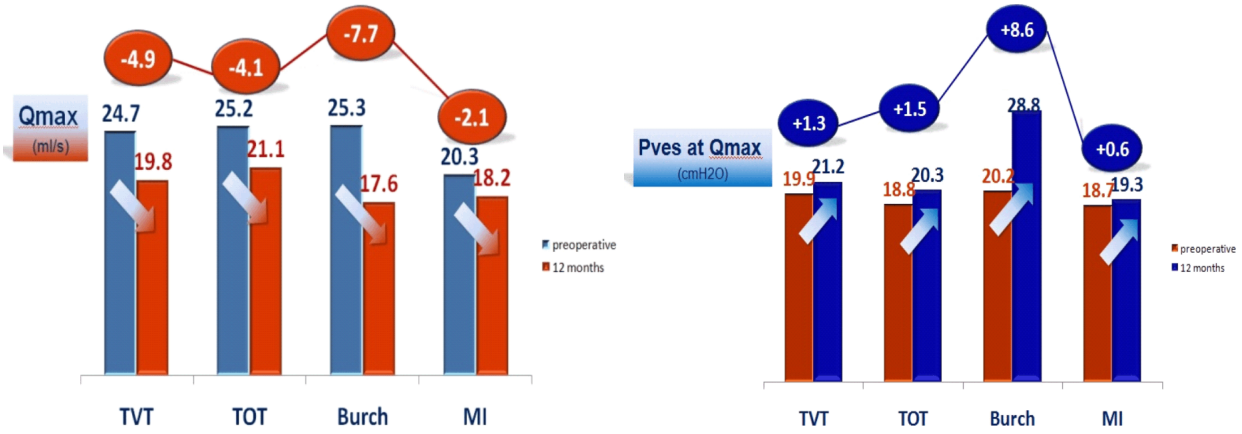

Figure 5 – ***Values of Qmax and vesical pressure at Qmax for different surgical techniques preoperative and at one year.***

Discussion

Selecting the patients with stress urinary incontinence caused by urethral sphincter deficiency is a difficult task. The important steps for recruiting patients in the study group are medical history, physical examination and urodynamic studies, which later 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.

Many variables as age, performance and estrogen status, surgical history, the severity of SUI have to be taken into account to create well-balanced study group.

In the future, based on clinical evidence and on the results obtained from patient's follow-up, randomized, multicenter, well-managed studies will be designed.

Suburethral slings, TVT, were introduced in the management of SUI several years ago. These procedures were performed by urogynecologist despite the absence of long-term data regarding efficiency, tolerance and the rate of healing. In the same manner, TOT's (trans-obturator tapes) were introduced and, although the medium and long-term data were lacking, they took over IVS slings and became the gold-standard treatment for SUI in women.

Muscle-derived stem cells (MDSC) therapy has advantages over current treatments for SUI. The use of cells are derived from the muscle tissue of the patient (autologous cell transplantation) therefore will not cause an immunogenic or allergic reaction and may persist longer than injected foreign substances such as collagen [10, 11]. MDSCs are uniquely different from fibroblasts and smooth muscle cells since MDSCs will fuse to form post-mitotic multinucleated myotubes. This would limit persistent expansion and risk of obstruction that may occur with other cell sources such as fibroblasts [12]. Finally, these cells form myotubes and myofibers that become innervated with the host muscle. Therefore, not only can they serve as a bulking agent, but also they are physiologically capable of improving urethral sphincter function [13–17].

Conclusions

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. 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 on the definition of "results", how they should be measured, follow-up intervals, etc. It seems that the development of myoblasts implant (if they will pass the time-proof test) could represent a breakthrough in treating this condition. As the pathogenesis of SUI is better understood and the development of tissue engineering technology advances, tissue engineering will play a more important role in the treatment of patients with SUI.

Acknowledgments

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