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VIDEO ARTICLE

Ultrasound-guided autologous myoblast injections into the extrinsic urethral sphincter: tissue engineering for the treatment of stress urinary incontinence

Mija Blaganje · Adolf Lukanović

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Abstract
Introduction and hypothesis Limitations of the existing treatment methods for stress urinary incontinence (SUI) have encouraged investigation of new therapeutic approaches in the field of regenerative medicine. Enabled by tissue engineering technology safety, feasibility and efficacy of ultrasound-guided intrasphincteric autologous myoblast implantation to treat SUI presented in the accompanying video were assessed in a pilot study of 38 women.
Methods Following upper arm muscle biopsy, autologous myoblast suspension was injected into the extrinsic urethral sphincter under transurethral ultrasound visualization. Functional electrical stimulation (FES) was used postoperatively to possibly enhance cell integration. Objective and subjective parameters were compared at 6 weeks, 3 months, and 6 months postoperatively.
Results The tissue harvest, laboratory tissue processing, and myoblast implantation were successful in all 38 patients. No serious adverse events were reported through the course of the study. Objective and subjective measurements collected at baseline were significantly improved at 6 weeks postoperatively. Additional improvement or a plateau was observed at 3 and 6 months postoperatively, not being negatively influenced by discontinuation of FES. Of the patients, 23.7 % considered their SUI cured, and 52.6 % reported improvement at 6 months; 95 % would recommend this treatment to others.
Conclusions Intrasphincteric ultrasound-guided autologous myoblast injection for SUI is feasible. This simple to perform and well-tolerated minimally invasive procedure safely produced promising initial results.

Keywords Myoblasts · Stress urinary incontinence · Tissue engineering · Skeletal muscle-derived cells · Progenitor cells

Aim of the video

The integrity of the extrinsic urethral sphincter, an omega-shaped striated muscle which compresses the urethra voluntarily, is necessary to maintain continence [1]. However, vaginal delivery, surgical injury, and aging may affect its morphologic and functional integrity [2]. Methods to treat stress urinary incontinence (SUI), a highly prevalent condition in women, have long existed, but their limitations have encouraged researchers to investigate new approaches, including those of tissue engineering, an emerging branch in the field of regenerative medicine, in order to preserve or improve tissue function. To avoid an ethical dilemma about embryonic stem cells, the search has concentrated on the potential use of autologous progenitor cells from adult tissues. We hereby present a video on ultrasound-guided intrasphincteric autologous myoblast implantation to treat SUI.

Methods

Study design

The study was approved by the National Medical Ethics Committee and National Agency for Medicinal Products and Medical Devices (registered at EU Clinical Trials

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M. Blaganje (✉) · A. Lukanović
Department of Gynecology, University Medical Centre Ljubljana, Šlajmerjeva 3,
1000, Ljubljana, Slovenia
e-mail: mija.blaganje@gmail.com

database, EudraCT No. 2009-012389-30 and ClinicalTrials.gov identifier: NCT01355133). All procedures were conducted in accordance with the National Act on Quality and Safety of Human Tissues and Cells for Purposes of Medical Treatment. All women gave informed consent to participate. The study design was an academic, investigator-initiated, non-comparative, single center explorative clinical trial. Special emphasis was placed on safety and feasibility.

Patients

By September 2010, 38 women had been treated in a period of 1 year. Women aged 18–75 years (median 50 years) with primary symptoms of SUI, normal detrusor activity on filling cystogram, and bladder capacity of over 300 ml, who failed prior noninvasive treatment, were eligible. Major exclusion criteria were severe urethral hypermobility, defined as a 45° rotation of the proximal urethra and bladder neck during a Valsalva maneuver and detected by the movement of an inserted Q-tip, uterine or vaginal descensus (>stage I according to the Pelvic Organ Prolapse Quantification system), and previous anti-incontinence surgery.

Biopsy

First the participants underwent an open cut muscle biopsy under local anesthesia to obtain a small (~0.5 cm^3) muscle tissue portion from the upper arm of the nondominant hand. The biopsy was placed in transport medium and sent to a Good Manufacturing Practice (GMP) certified institution (Innovacell Biotechnologie AG, Innsbruck, Austria) for myoblast isolation, cultivation, harvest, and storage.

Implantation

Patients underwent autologous myoblast implantation 5–14 weeks after the biopsy. In an operating theater a specially designed injection device (Sonoject, A.M.I., Feldkirch, Austria) with a rotating, high-frequency transurethral 8F ultrasound probe was inserted into the urethra to first visualize the extrinsic urethral sphincter and to precisely inject 2 ml of liquid myoblast suspension (1×10^6–5×10^7 cells) divided into 26 small depots of 50–100 μl each in two different levels of the sphincter. Upon completion of the implantation procedure, hypoechogenic spots were observed in the extrinsic urethral sphincter. The first 18 cases were performed under i.v. anesthesia and all subsequent cases under local lidocaine gel anesthesia with i.v. analgesia.

Functional electrical stimulation

Immediately following the myoblast implantation, the participants self-administered functional electrical stimulation (FES) transvaginally at home for 5 weeks to enhance cell integration [3]. The device used according to the manufacturer's instructions was the contic+ (tic Medizintechnik, Dorsten, Germany). However, to ensure that any clinical improvement 6 weeks after the implantation would not be due to FES alone, the participants had previously undergone a first 5-week FES cycle, just after muscle tissue was harvested. The objective and subjective measurements obtained

Table 1 Characteristics of patients treated with autologous myoblasts at baseline and at 6 weeks, 3 months, and 6 months following implantation

	Baseline	Postimplantation			
		6 weeks	3 months	6 months	*P*
No. of patients	38	37	30	38	
UIE	13 (4–41)	5 (0–33)	3(0–33)	4(0–35)	<0.0001
UIS	24 (4–67)	5 (0–33)	3 (0–33)	4 (0–45)	<0.0001
I-QOL	57 (28–92)	78 (41–105)	86 (50–109)	89 (32–110)	<0.0001
VAS	8 (3–10)	3 (0–9)	3(0–10)	3 (0–10)	<0.0001
Stress test negative	0	29	–	23	<0.0001
Pad test negative	0	–	–	25	<0.0001

The numeric variables are presented as median values (range) or number of patients. *P* values are for any of the postimplantation outcomes vs baseline

UIE episodes of urinary incontinence from a 3-day voiding diary, *UIS* amount of leaked urine measured semiquantitatively from a 3-day voiding diary, *I-QOL* Incontinence Quality of Life Questionnaire sum score: range 22 (worst) — 110 (best), *VAS* visual analog scale of the degree of trouble score: range 0 (best) — 10 (worst)

upon completion of each FES cycle were then compared [4] and further evaluated at 3 and 6 months following implantation.

Assessment

To ensure safety, vital signs and common laboratory values for urine and blood were monitored. Moreover, particular attention was paid to possible onset of complications of the muscle tissue harvest and myoblast implantation, such as surgical injury, local inflammation, urinary tract infection, pelvic pain, urinary retention, voiding dysfunction, de novo urgency, hyperplasia, and tumor formation. Physical examination, fixed bladder volume stress test result, pad test result, entries in the 3-day voiding diaries for urinary incontinence episodes (UIE) and for the amount of leaked urine during incontinence episodes measured semiquantitatively (UIS), degree of trouble living with SUI on a visual analog scale (VAS), score on the modified Patient Global Impression of Improvement scale (PGI-I), and score on the Incontinence Quality of Life questionnaire (I-QOL) were recorded at baseline, after completion of the first FES cycle that followed the muscle tissue harvest, 6 weeks after the myoblast implantation, after the second FES cycle was completed [4], 3 months, and 6 months following implantation.

Results

Thirty-eight women with a median age of 52 years, median parity of 2 (range 1–4), and mean body mass index (BMI) of 26.6 kg/m^2 (SD±4.4) at baseline were treated.

All phases of the procedure were performed by a gynecologist. The first cases of biopsies were supervised by a plastic and reconstructive surgeon, whereas initial implantations were supervised regarding sphincter identification and depot positioning by a radiologist directly or indirectly through recordings overview. The mean duration of biopsy was 10 min and the mean duration for implantation 15 min. Cell harvest performed by the laboratory was successful in all of the patients.

No serious adverse events were reported throughout the course of the study. In terms of safety no declines from average regarding physical examination, lab values, or vital signs were detected, with the exceptions of one subject being referred to physiotherapy due to local transitory tenderness at the biopsy site at the time of the implantation and another two with acute cystitis at 6 weeks following implantation. The conditions all resolved with therapy. No postimplantation urinary retention was measured (defined as post-void residual urine volume greater than 50 ml), nor were there any cases of de novo urgency, hyperplasia, or tumors.

Compared with the objective and subjective measurements collected at baseline and after the preimplantation FES cycle, the corresponding measurements obtained 6 weeks following implantation, after the completion of a second FES cycle, indicated considerable improvement [4], which was later not negatively influenced by discontinuation of FES. Additional improvement or a plateau was observed at 3 and 6 months following implantation (Table 1). Of the patients, 9 (23.7 %) considered their SUI cured, and 20 (52.6 %) reported improvement at 6 months; 95 % would recommend this treatment to others.

Conclusion

Intrasphincteric ultrasound-guided autologous myoblast injection for SUI is feasible. This simple to perform and well-tolerated minimally invasive procedure safely produced promising initial results.

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Conflicts of interest None.

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