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INTRASPHINCTERIC AUTOLOGOUS MYOBLAST INJECTION FOR THE TREATMENT OF STRESS URINARY INCONTINENCE

Hypothesis / aims of study
Stem cell therapy for the regenerative repair of the deficient extrinsic urethral sphincter has been at the forefront of incontinence research. The purpose of this study was to evaluate safety, tolerability and efficacy of ultrasound guided transurethral intrasphincteric autologous myoblast injections in the treatment of female patients with stress urinary incontinence.

Study design, materials and methods
38 female patients treated through a period of 11 months concluded the trial by February 2011. Patients with primary symptoms of SUI, normal detrusor activity on filling cystogram and bladder capacity of over 300 ml, who failed prior non-invasive treatment at least 3 months prior to enrolment, were eligible. Marked hypermobility, uterine or vaginal descensus and previous anti-incontinence surgery were the major criteria of exclusion. Skeletal muscle portion was obtained from a small open cut biopsy of the non-dominant biceps muscle and shipped to a remote Good Manufacturing Practice (GMP) certified cell-processing laboratory for myoblast isolation and expansion. Autologous myoblast suspension was injected under transurethral ultrasound guidance in a uniform pattern directly into the extrinsic urethral sphincter through a combined transurethral ultrasound device. Electrical stimulation (ES) was undertaken upon patients to enhance cell integration and new muscle tissue formation following myoblast injection. An identical cycle of ES in duration of 5 weeks was applied before and after myoblast implantation. The findings of 5 follow-up visits were compared at baseline, upon termination of the first ES cycle before myoblast implantation (effect of ES without myoblasts), upon termination of the second ES cycle at 6 weeks following myoblast implantation (effect of combination of myoblasts and ES), 3 and 6 months post-implantation.
In terms of safety assessment adverse events, lab values of urine and blood investigations and vital signs were monitored. Particular attention was paid to eventual immediate and later-onset complications of biopsy and cell injection, including surgical injury, urinary tract infection, inflammation and pelvic pain, urinary retention, voiding dysfunction, *de novo* urge incontinence, hyperplasia or tumors.
Physical examination, fixed bladder volume stress test, pad test, 3-day bladder diaries for urinary incontinence episodes (UIE) and amount of leaked urine measured semiqantitative (UIS), visual analog scale of the degree of suffering (VAS), modified patient global impression scale (PGI-I), quality of life questionnaire (I-QOL) and other were utilized to assess outcomes.
Statisticaly significant differences across measurement points of follow-up visits were assessed with pairwise Wilcoxon Signed Rank tests.

Results
38 women of the median age 52 years, median parity of 2 (range 1-4) and mean BMI of 26.6 (SD±4.4) at baseline were treated. No serious adverse events were reported through the course of the study. In terms of safety no declines from average were detected, with an exception of one referral to physiotherapy due to local transitory biopsy site tenderness and acute cystitis occurring once and twice in two different patients. All conditions resolved with therapy. Early pregnancy in one patient identified on ultrasound scan at 6 months resulted in term delivery of a healthy baby.
At 6 weeks post-implantation the median UIE, UIS, VAS and I-QoL scores all significantly improved in regard to baseline ($p<0.000$ for all parameters) and preoperative ES ($p<0.000$ for all parameters). Though not significant, additional improvement was observed over time at 3 and 6 months following implantation.
At 6 months post-implantation patients assessed tolerability of the procedure as a median 4 (very good) and effectiveness as 3 (good) on a scale 1-5. According to the modified PGI-I 9 (24%) were cured, 20 (54%) improved and 12 (32%) unchanged. Negative stress test was observed in 61% of the treated population and negative pad test in 66% respectively. 95% of patients would recommend the treatment to others.

Interpretation of results
The present results showed this procedure to be safe and well tolerated. The onset of improvement was seen at 6 weeks following myoblast implantation. The combination of myoblasts and ES was clearly better then ES alone, implying cell therapy effect. Hence, termination of ES had no negative influence upon improvement, which was observed over the course of 6 months.

Concluding message
Intrasphincteric transurethral ultrasound guided autologous myoblast injection is a relatively simple and precise new minimally invasive SUI treatment approach of promising therapeutic potential.

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**EudraCT, Number 2009-012389-30**
Is this a Randomised Controlled Trial (RCT)?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**NATIONAL MEDICAL ETHICS COMMITTEE**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**