

PERIURETHRAL INJECTION OF AUTOLOGOUS ADIPOSE-DERIVED REGENERATIVE CELLS FOR THE TREATMENT OF MALE STRESS URINARY INCONTINENCE: OUTCOME OF PRELIMINARY CLINICAL TRIAL

Hypothesis / aims of study

We previously demonstrated the rationale and efficacy of periurethral injection of the cultured adipose-derived stem cells (ASCs) for treatment of stress urinary incontinence (SUI) in the animal experiment [1]. However, the keys to clinical application of cell therapy are the usage of autologous cells and the procurement of enough cells without the need for cell culture. Using adipose-derived regenerative cells (ADRCs), we created a novel treatment strategy to regenerate the urethral sphincter that meets these criteria (Fig.1) [2]. We conducted a first in-man study to assess the effects of periurethral injection of autologous ADRCs on male patients with SUI caused by urethral sphincter deficiency.

Study design, materials and methods

Fourteen male patients with persistent SUI after prostate surgery (radical prostatectomy in 11 patients, and holmium laser enucleation of the prostate; HoLEP in 3) were included in this preliminary clinical trial. After liposuction of 250 mL of adipose tissue from the abdomen, we isolated ADRCs from this tissue by using the Celution™ system. Subsequently, these ADRCs and a mixture of ADRCs and adipose tissue were transurethrally injected into the rhabdosphincter and submucosal space of the urethra, respectively. Unlike other cell therapies, this treatment is entirely autologous, does not require cell culture, and is performed as a single surgical procedure. Primary outcome was assessed at by a 24-hour pad test, at baseline, 2 weeks, 1, 3, 6, 9, and 12 months after treatment. Secondary outcomes included a validated patient questionnaire (ICIQ-SF; International Consultation on Incontinence Questionnaire-Short Form), urethral pressure profile, contrast-enhanced transrectal ultrasonography, and magnetic resonance imaging (MRI). Eleven patients (post-radical prostatectomy in 9 and post-HoLEP in 2) were followed-up longer than one year (mean 26 months, 12 to 45 months). We report the outcomes on efficacy and safety of the treatment at one-year follow-up in these 11 patients.

Results

After injection, urinary incontinence progressively improved in 8 of the 11 patients during the one-year follow-up, i.e., decreased leakage volume was observed in a 24-hour pad test. One patient with moderate incontinence achieved total continence at 14 weeks after injection. In the 8 patients who showed improvement, the mean daily leakage for 4 days of consecutive measurements gradually improved from 230.4 to 100.5 g at one year after injection (Fig. 2). The ICIQ-SF total score improved from 13.8 to 11.1 points. In the urethral pressure profile, the maximum urethral closing pressure (MUCP) and functional profile length (FPL) increased from 34.8 to 45.0 cmH₂O and from 16.4 to 26.0 mm, respectively. In 3 patients without improvement in leakage volume, the mean leakage amount per day, total ICIQ-SF score, MUCP, and FPL changed from 441.8 to 473.7 g (Fig. 2), 19.7 to 19.7 points, 34.0 to 43.7 cmH₂O, and from 19 to 23 mm, respectively. MRI showed sustained presence of the injected adipose tissue in all patients. Enhanced ultrasonography showed a progressive increase in blood flow to the injected area up to 6 months after the injection in all patients. No significant adverse events were observed peri- or post-operatively.

Interpretation of results

The periurethral injection of ADRCs gradually improved SUI over time. The results of the present clinical trial and previous experimental study [1] suggested the mechanism involved in the improvement of the sphincteric function to be bulking effect, regeneration of the smooth muscle and increased blood flow caused by the injection of ADRCs.

Concluding message

The results of this preliminary study showed that periurethral injection of autologous ADRCs is a safe and feasible treatment modality for male patients with stress urinary incontinence caused by urethral sphincter deficiency.

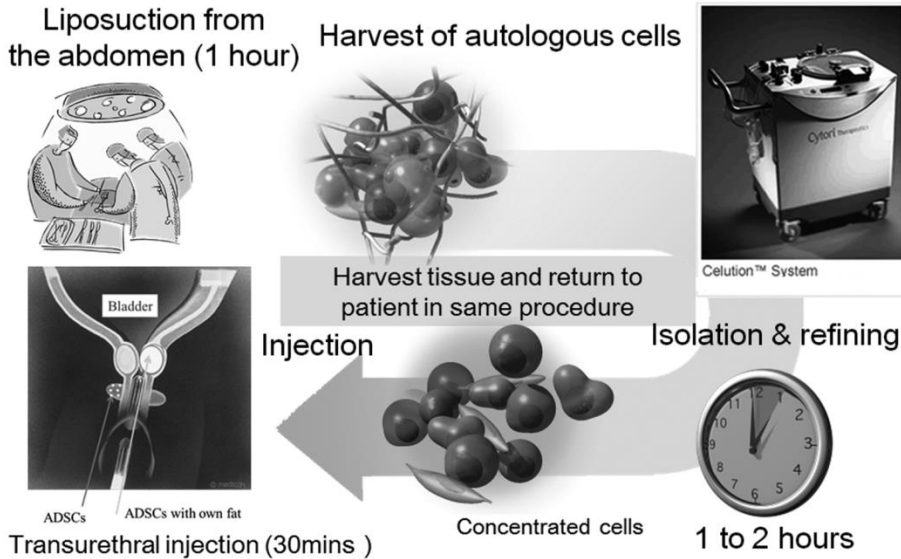


Fig.1 Flow diagram of periurethral injection of autologous ADRCs

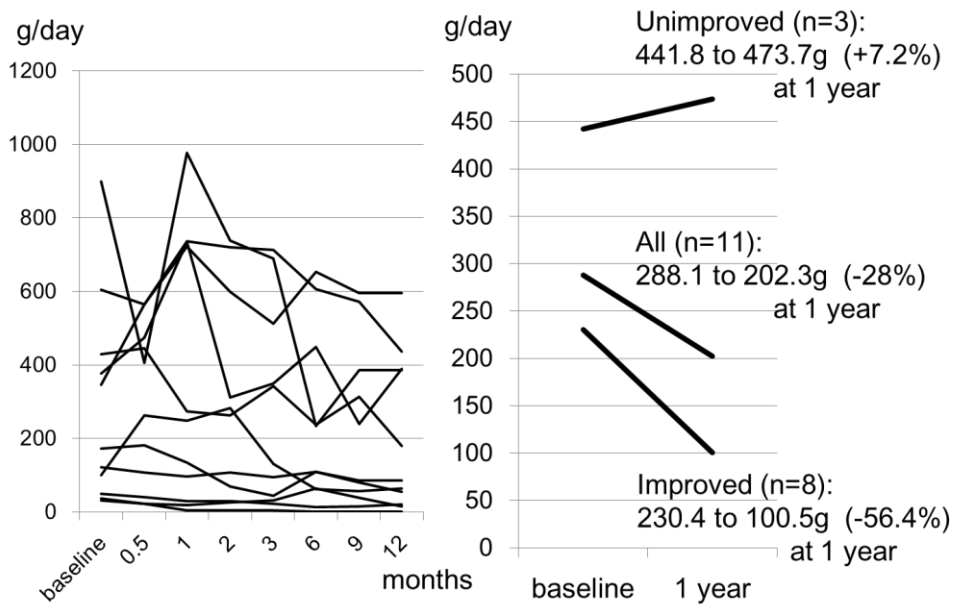


Fig.2 Changes of daily leakage volume after treatment

References

1. Watanabe T. Int J Urol, 18:659-666, 2011
2. Yamamoto T. Int J Urol, 19:652-659, 2012

Disclosures

Funding: none **Clinical Trial:** Yes **Public Registry:** No **RCT:** No **Subjects:** HUMAN **Ethics Committee:** Ethics committee of Nagoya University Graduate School of Medicine, Committee of Japanese Ministry of Health, Labor and Welfare, according to the guideline on Clinical Research using Human Stem Cells **Helsinki:** Yes **Informed Consent:** Yes