European Journal of Obstetrics and Gynecology 278 (2022) 38–44

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Suburethral implantation of autologous regenerative cells for female stress urinary incontinence management: Results of a pilot study

Anne Maene [a,*], Gulcan Deniz [b], Cyril Bouland [a,c,d], Laurence Lagneaux [d], Pierre Philippart [a,e], Fréderic Buxant [b]

[a] Université Libre de Bruxelles, Medicine Faculty, route de Lennik 808, 1070 Brussels, Belgium
[b] Departments of Gynecology and Obstetrics, IRIS South Hospital, rue Jean-Paquot 63, 1050 Brussels, Belgium
[c] Departement of Stomatology and maxillofacial Surgery, CHU Saint-Pierre, 322 Rue Haute, 1000 Brussels, Belgium
[d] Laboratory of Clinical Cell Therapy, Jules Bordet Institute, Université Libre de Bruxelles, campus Erasme, Route de Lennik 808, 1070 Brussels, Belgium
[e] Departement of Stomatology and maxillofacial Surgery, IRIS south Hospital, rue Docteur Huet, 1070 Brussels, Belgium

ARTICLE INFO

Keywords:
Cell therapy
Adipose-derived stem cells
Platelet-rich-fibrin
Stromal vascular fraction
Stress urinary incontinence

ABSTRACT

Objectives: To assess the feasibility and the safety of treating female stress urinary incontinence (SUI) with suburethral implantation of a mixture of the stromal vascular fraction from adipose tissue and leukocyte-and platelet-rich-fibrin.

Methods: Patients with SUI were treated with a mixture of stromal vascular fraction and leukocyte-and platelet-rich fibrin. The stromal vascular fraction was obtained from enzymatic digestion of autologous adipose-tissue and added to an leukocyte-and platelet-rich-fibrin membrane. The mixture was transvaginally implanted into the suburethral area. A fraction of the Stromal vascular fraction sample was used for cellular characterization. Patients were followed for 9 months. Every 3 months, the patients were clinically evaluated with a cough- stress test and a validated-questionnaire. An MRI was performed preoperatively and 3 months after the procedure to assess tissue changes.

Results: Ten patients received the surgical procedure. The validated-questionnaire revealed a subjective SUI improvement in nine patients 3 months after the operation and in seven patients 9 months after the operation. Eight, six, and four patients achieved a negative cough-stress test 3, 6 and 9 months post-injection, respectively. Flow cytometric analysis of stromal vascular fraction cell phenotypes revealed predominantly mesenchymal and endothelial cell heterogeneity. In total, we injected 0,18 $\times$ 10^6 to 13,6 $\times$ 10^6 cells. No adverse events were observed *peri-* or postoperatively.

Conclusion: These preliminary results suggest that the suburethral implantation of a combination of SVF and L-PRF is a feasible and safe modality for treating female SUI. However, evidence is lacking and further research are needed to clarify the respective roles of SVF and L-PRF in female SUI treatment.

Introduction

Stress urinary incontinence (SUI) is an underdiagnosed health-problem that impacts quality of life (QOL). Midurethral-slings are the gold-standard surgical treatment for female-SUI. However, this surgical-technique isn't without complications and exposes the patient to inherent morbidities resulting from the use of heterologous equipment. The rate of complications related to prosthetic material is controversial within the National Institute for Health and Care Excellence, calling into question the safety of surgical meshes for urogynecological disorders [1].

Cell-therapy may offer an alternative to midurethral-slings and broaden the therapeutic options for SUI. The stromal-vascular-fraction (SVF) is isolated by enzymatic-digestion of adipose-tissue (AT) followed by centrifugation. This yields a heterogeneous-cell mixture containing mesenchymal-stromal-cells (MSC), fibroblasts, endothelial

Abbreviations: ADSC, adipose-derived stem cells; APC, autologous platelet concentrates; AT, adipose tissue; ICIQ-SF, International Consultation on Incontinence Questionnaire-short Form; L-PRF, Leukocyte- and platelet-rich fibrin; MSC, Mesenchymal stem cells; MRI, magnetic resonance imaging; PRP, Platelet-rich plasma; QOL, quality of life; SVF, Stromal vascular fraction; SUI, Stress urinary incontinence.

* Corresponding author.
E-mail address: anne.maene@ulb.be (A. Maene).

https://doi.org/10.1016/j.ejogrb.2022.08.028
Received 19 February 2022; Received in revised form 23 August 2022; Accepted 30 August 2022
Available online 9 September 2022

precursor-cells and hematopoietic-cells [2]. MSC display proliferative, differentiation, immunomodulatory and trophic properties [3]. MSCs derived from bone-marrow, skeletal-muscle, and AT have been tested as treatments for SUI, showing positive effects on urethral function [4,5]. AT represents a rich source of MSC, 100-fold more abundant than in the bone-marrow [6]. In addition to this abundance, AT is an attractive source for cell-therapy because it only requires a minimally invasive harvesting procedure.

Multiple experimental studies [7–10] have shown that MSCs derived from AT, called adipose-derived-stem-cells (ADSC), are multipotent cells capable of myogenic and neurogenic differentiation in vitro [5,11]. In animal model, ADSCs injections have been shown to restore urethral function and induce myogenic differentiation, nerve regeneration, and angiogenesis at the site of implantation [5]. Six clinical studies using ADSCs to treat SUI have shown encouraging results [12–17] and significant functional improvement in urethral function [18]. Several studies have compared the therapeutic effects of ADSCs and SVF-cells and found similar therapeutic effects [19–21]. We studied the implantation of AT-derived SVF-cells for managing female-SUI.

To avoid possible dispersion and migration of SVF-cells, we injected the cells in a membrane enriched with leukocyte- and platelet-rich-fibrin (L-PRF). L-PRF is a concentrate of autologous-fibrin that is obtained by simple centrifugation of a blood sample. The solid membrane serves as a matrix to contain SVF-cells and promote the local proliferation and differentiation of MSCs by the release of growth-factors over at least 7 days [22].

To our knowledge, there has never been a study using the combination of SVF/L-PRF suburethral in the treatment of SUI. We suspect that SVF/L-PRF could have a synergistic impact on SVF survival, as suggested in some experimental studies [23,24]. This pilot study's aim is to evaluate the feasibility and the safety of the innovative approach for female SUI-management.

Methods

The medical protocol and ethics of this study followed the Declaration of Helsinki. It was approved by the ethics-committee of Erasmus-Hospital, University-Clinic of Brussels (P2019/485/CCB B406201941726) and IRIS-South-Hospitals (CEHIS/2019-15).

This prospective, non-randomized, single-center clinical trial took place between June 2019 and May 2020. Patients were recruited from the Joseph-Bracops-Hospital and informed of possible treatment alternatives.

All participants were adult and had a history of failed conservative treatment such as physiotherapy. They presented SUI for more than 6 months associated with an impact on QOL. Exclusion criteria included history of active malignant pathology, mental disorders making them unable to give consent, neurogenic urinary-incontinence, a history of surgery for the treatment of SUI, pelvic-organ prolapse, and detrusor overactivity on urodynamics.

After written informed consent, patients underwent the following at baseline and during follow-up: a cough-stress test to confirm the SUI diagnosis, a urodynamic evaluation, a pelvic-MRI, and the International-Consultation-on-Incontinence-questionnaire-Short-Form (ICIQ-SF) [25]. This validated-questionnaire assesses subjective symptoms, such as frequency, amount of urine-loss and impact on QOL. A total score out of 21 points is calculated. A score above 13/21 indicates a severe state.

The average operating time was one hour-and a half. The procedure consisted of a single surgery under general-anaesthesia that included an AT harvest and its enzymatic treatment to obtain the SVF, a blood sample to prepare L-PRF, and suburethral implantation of the SVF/L-PRF. For implantation, the surgeon created a 1 cm mid-suburethral incision and performed a paraurethral dissection with a fine scapel. The SVF/L-PRF was affixed at the incision level.

The patients were followed for 9 months with weekly follow-up during the first month then follow-ups every 3 months. Pelvic-clinical exams were used to assess complications and SUI-improvement. Every consultation, patients performed a cough-stress-test with a filled bladder to objectively measure treatment efficacy. Three months after the procedure, patients underwent a pelvic-MRI to evaluate the thickness of the urethral wall at its mid-height and 1 cm above its external-orifice (implantation site).

Cough stress test procedure

We asked our patients to urinate before coming to the visit and to drink 2glasses of water (50 cl) while they were waiting. We asked them before doing the test if they felt subjective fullness. These instructions were the same in pre and post-operation. This test was performed in the supine position after a series of forceful-coughs and then, in case of negativity, in the standing position.

AT collection and SVF preparation

A 30 mL sample of AT was collected from the abdominal-fat panicle by liposuction using a standard multi-hole infusion 3 mm-cannula. Fat was harvested with mechanical aspiration. The sample was digested with the Liberase-MTF-C/T, GMP-Grade-Kit (Creative-enzymes-lot 28572622) for 30 min at room-temperature and centrifuged at 800xg for 5 min. The SVF-pellet was washed with saline solution, and a fraction was characterized at the Laboratory of Clinical-Cell-Therapy of the Jules-Bordet-Institute of the Université libre de Bruxelles (Fig. 1).

L-PRF preparation

A blood-sample was taken by peripheral-venous puncture into 9 mL glass collection tube, without any anticoagulants. The blood was immediately centrifuged (Intra-Spin EBA 200, Intra-Lock-System, Florida, USA) for 12 min at 400xg (2700 rpm) to obtain the L-PRF [26]. (Fig. 2). The harvested-SVF was injected into the L-PRF, taking advantage of its three-dimensional properties. (Fig. 3).

SVF characterization

Flow-cytometric-analyses were performed at the Laboratory of Clinical-Cell-Therapy to determine the cellular subpopulations within the SVF using cellular expression of CD31, CD34 and CD45. This allowed for the determination of the percentages of stromal ($CD31^-CD34^+CD45^-$) and endothelial-cells ($CD31^+CD34^+CD45^-$). Within the SVF, several studies have characterized ADSCs, excluding hematopoietic and endothelial-cells based on these marker combinations [27]. We chose the combination $CD45^-/CD31^-/CD34^+$ to evaluate the percentage of ADSC in the SVF. Cell phenotyping was performed immediately after the SVF harvest. The cells were incubated with the appropriate fluorescently conjugated-antibodies for 30 min at room-temperature in the dark. Data was acquired on a MACSQuant-Analyzer (Miltenyi Biotec) and analyzed with FCS-Express-4-software (DeNovo-Software). The number of MSCs in the SVF-sample is evaluated by Colony-forming unit-fibroblast (CFU-F) assay.

Statistical analyses

A descriptive-analysis of the results was conducted. Statistical analysis of the ICIQ-SF questionnaire data used a paired Wilcoxon-test. The threshold for significance was 0.05. Statistical analysis is performed using SPSS®software.

Results

Ten patients were included in, and completed the study. The average age was 47 ± 3 years. Three patients presented a history of pelvic-surgery (salpingectomy or hysterectomy). Five were postmenopausal

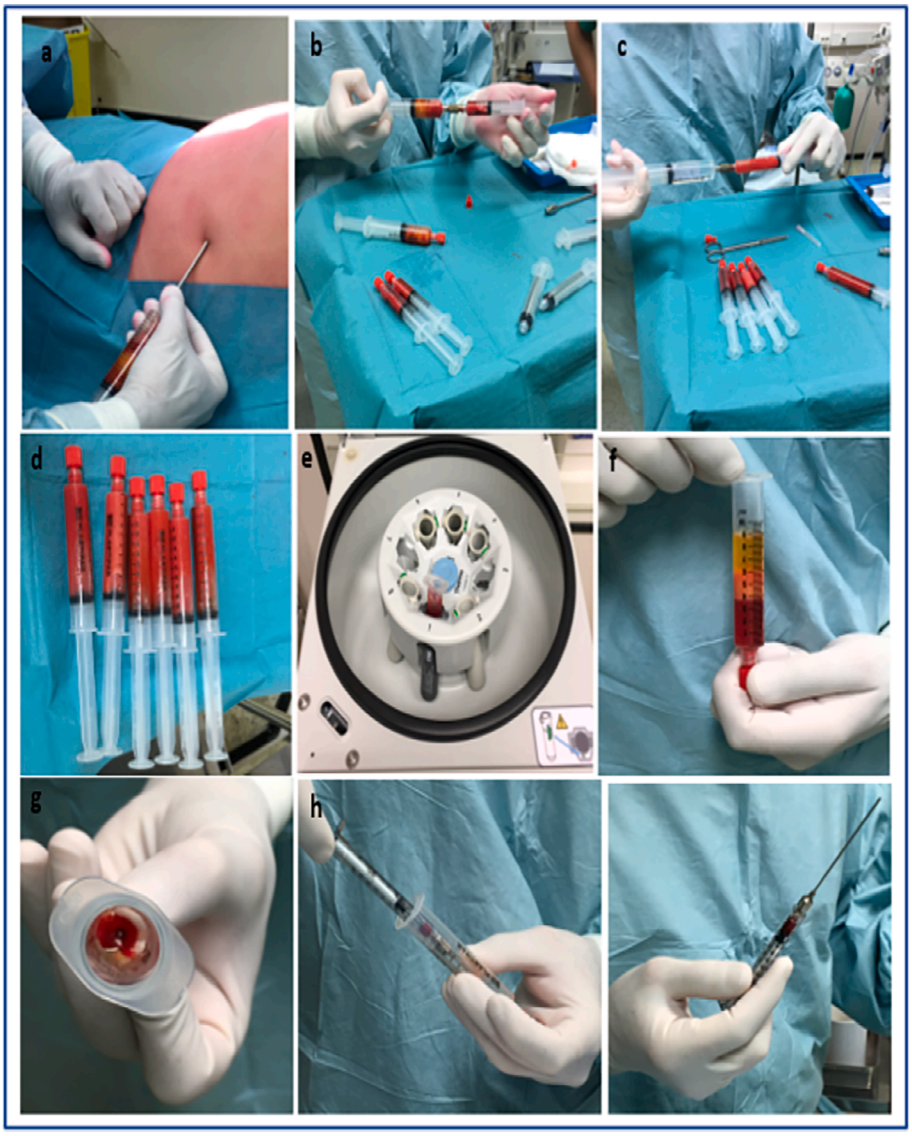

Fig. 1. Stromal Vascular Fraction preparation.

and six were overweight (BMI > 25). All patients presented SUI associated with urethral-hypermobility without associated prolapse. None had sphincter insufficiency based on the urodynamic-assessment (Table 1).

The subjective-symptom assessment by ICIQ-SF is shown in Fig. 4. Three months after the procedure, we observed a significant-improvement in the QOL (p =.007) along with a significant-decrease in the quantity (p =.005) and frequency (p =.007) of incontinence in nine patients. Six months after the procedure, four patients no longer had urine-loss. Eight patients presented with significant-improvement in the quantity (p =.010) and frequency (p =.011) of urine-loss and their QOL (p =.012) and total ICIQ-SFscore (p =.008). Nine months after the procedure, two patients didn't have urine-loss, and seven still had significant-improvement in the quantity of urine-loss (p =.039), QOL (p =.034), and total ICIQ-SF score (p =.038). The improvement in the frequency of urinary-loss was no longer significant (p =.101).

The results of the filled bladder cough-stress-test showed that eight, six and four patients had a negative-test 3,6 and 9 months after the procedure. At the end of the observation, four patients were satisfied and didn't desire further intervention. Two of the patients benefited from an midurethral-sling procedure after the 9-months follow-up.

Patients received an MRI before and after the intervention to evaluate the results of the operation (Table 2). No significant change in urethra-thickness was observed between the preoperative and 3-month follow-up data (p =.795). Nevertheless, we observed a change in the appearance of the periurethral-tissue with postintervention radial densification in eight patients, clearly visible in patient#5 (Fig. 5). No patient experienced any side-effects of the suburethral SVF/L-PRF injection.

In vitro results

Analysis of the SVF-cell populations by flow-cytometry revealed predominantly mesenchymal and endothelial-cell heterogeneity (CD146:24,44 %±8,13; CD34:13,11 %±5,7; CD90: 15,36 %±6,8; CD29: 17,11 %±6,47; Fig. 6).

In total, 0,18 × 10^6 to 13,6 × 10^6 cells were injected per patient. In vitro, SVF-culture confirmed the presence of MSCs and their ability to expand. However, no growth was observed in two patients (#1 and #2) due to the low number of cultured-cells. Significant growth was noted for patient#3. For the other cases, 5 × 10^6 SVF-cells expanded to between 0.9x10^6 and 7,58 × 10^6 cells (Fig. 7). The number of mesenchymal-progenitors, estimated by the CFU-F technique, varied from 2,9 to 6900 colonies per 10^6 SVF-cells. We observed a mean ADSC

Fig. 2. Leukocyte-and platelet-rich Fibrin preparation (L-PRF).

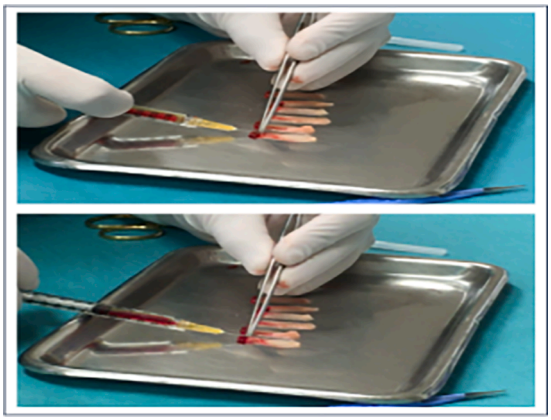

Fig. 3. SVF is injected inside L-PRF.

level of 7.2 ± 2.8 % in the SVF (n = 10).

Discussion

AT is one of the top MSC-sources because of its accessibility and abundance. To isolate ADSCs, a lipoaspiration is enzymatically digested and centrifuged to produce a cell-pellet known as the SVF. ADSC enrichment involves culturing the SVF-pellet in vitro. However, culture requires time, is expensive and presents a contamination-risk, rendering ADSCs unsuitable for clinical use.

We therefore studied the implantation SVF-cells to manage female-SUI. The SVF is a dynamic-mixture that interact to modulate the immune response, adapt to the host-microenvironment, and promote vasculature. These easily obtained, uncultured, heterogeneous SVF-cells are a therapeutic alternative to cultured ADSCs and have versatile applications in regenerative medicine [28]. We hypothesized that SVF/L-PRF could restore suburethral support based on the mechanism of midurethral-slings. The SVF could promote muscular-regeneration and

Table 1
Patient characteristics.

Patients	Age	BMI†	G/P‡	Medical background	Incontinence type according to Stamey's classification	Duration of SUI (months)	POP-Q staging §	MUCP ¶ (cmH_2O)
1	44	27.1	G3P3	Premenopausal.	SUI:stage 2	12	Aa-2,Ap-2,Ba-2,Bp-2, C-7, D-7, tvl 9, gh3	42
2	36	21.6	G4P3	None.	SUI:stage 1	12	Aa-2,Ap-2,Ba-2,Bp-2, C-7, D-7, tvl 9, gh3	47
3	34	28.3	G1P1	1 cesarian.	SUI:stage 2	12	Aa-2,Ap-2,Ba-2,Bp-2, C-7, D-7, tvl 9, gh3	58
4	53	20,7	G4P3	Salpingectomy, 3 cesarian, menopause since 52 years old	SUI:stage 2	6	Aa-3,Ap-3,Ba-3,Bp-3, C-8, D-8, tvl 9, gh3	47
5	57	20,9	G2P2	Menopause since 45 years old	SUI:stage2	12	Aa-3,Ap-3,Ba-3,Bp-3, C-8, D-8, tvl9, gh3	41
6	49	28.5	G2P2	Arterial hypertension	SUI: stage 1	12	Aa-3, Ap-3, Ba-3, Bp-3, C-8,D-8, tvl9, gh3	47
7	52	27.9	G3P3	Arterial hypertension, chronic obstructive pulmonary disease, hysterectomy (2016), Menopause since 51 years old	SUI: stage 2	12	Aa-2, Ba-2, Ba-2, Bp-2, C-7, D-7, tvl8, gh3	58
8	51	29.4	G2P2	Menopause since 50 years old	MIU:stage 2	6	Aa-2,Ba-2,Ap-2,Bp-2, C-7, D-7, tvl8, gh4	47
9	37	39.2	G5P2	Arterial hypertension, Hysterectomy (2018)	MIU: stage 2	6	Aa-2,Ap-2,Ba-2,Bp-2, C-7, D-7, tvl 9, gh3	57
10	59	29.2	G2P2	Menopause since 53 years old	MIU: stage 2	12	Aa 3, Ap3, Ba-3, Bp-3, C7, D7, tvl8, gh3	52

†: body mass index; ‡: G:gestity, P:parity; §: evaluation of pelvic organ prolapse; ¶: maximal urethral closure pressure; SUI: stress urinary incontinence; MIU: mixed urinary incontinence; MUCP: maximum urethral closing pressure.

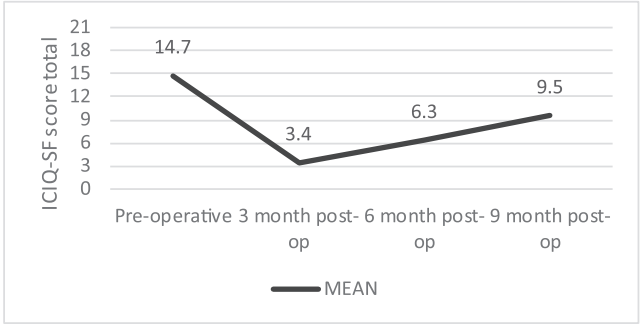

Fig. 4. Mean ICIQ-SF total score preoperatively and at 3, 6 and 9 months post-injection.

the urethral surrounding connective-tissue and L-PRF would play a dual role as a scaffold and a source of growth-factors. We predicted that suburethral-tissue regeneration would provide an adequate coaptation of the urethral-mucosa during abdominal thrust efforts.

At 3-month follow-up, MRI detected a modified periurethral-tissue appearance. Nine months after implantation, seven patients presented with an improved QOL, decreased urine-loss, and an improved ICIQ-SF total-score. In addition, four patients had a negative cough-stress-test. No intra- or postoperative complications were identified during the observation period.

No existing publication has treated SUI with a combination of SVF and L-PRF. Six clinical trials used ADSCs to treat SUI. These studies were of a low-level of evidence, with small-sample-sizes (3–13 patients) and a follow-up of 3–60 months. Furthermore, heterogeneity between the studies limits their comparison. Kuismanen and colleagues published the first ADSC treatment of female-SUI in 2014 [14]. Five patients benefitted from an transurethral injection of ADSCs combined with collagen-gel. The authors expanded the ADSCs for 3 days in culture to

Table 2
Results of pre- and postoperative MRI and cough stress test.

Patients	MRI pre-operative (mm)		3 months post- operative MRI (mm)		Cought-test				Post-operative complications	
	MH†	E0 ‡	MH	EO	Baseline	3 months	6 months	9 months	½ month	3,6, 9 months
1	4.99	5	5.26	5	+	–	–	–	None	None
2	4.54	5.1	6.05	5.1	+	–	–	–	None	None
3	5.1	4.3	7.1	5.4	+	–	–	–	None	None
4	4.60	4.80	5	5.2	+	–	–	+	Umbilical *peri*-ecchymosis	None
5	6.82	2.6	7.01	2.9	+	–	+	+	None	None
6	6.51	6.3	5.52	4.17	+	–	–	–	None	None
7	4.5	4	4	3.15	+	+	+	+	None	None
8	7.1	4.6	5.9	5.4	+	–	–	+	Umbilical *peri*-ecchymosis	None
9	4.2	4.6	4.5	4.8	+	+	+	+	Umbilical *peri*-ecchymosis	None
10	6.2	5.5	6.5	5.5	+	–	+	+	None	None

†: thickness of the urethra at mid-height (MH); ‡: thickness of the urethra 1 cm from the external opening (EO).

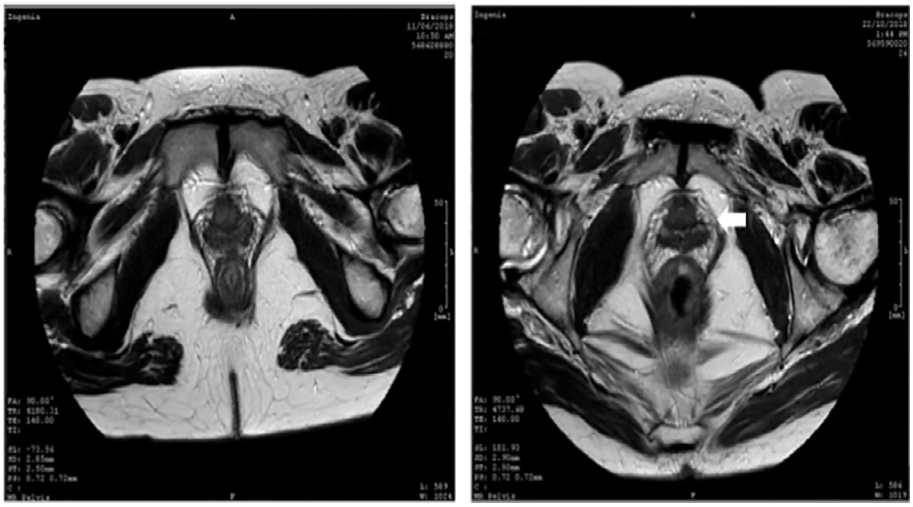

Fig. 5. Axial section of pelvic T1-MRI before and after stromal vascular fraction/ leukocyte- and platelet-rich fibrin injection in patient #5.

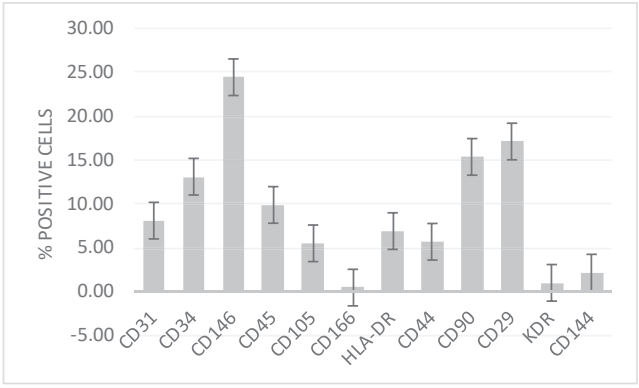

Fig. 6. Phenotypic characterization of the stromal vascular fraction by flow cytometry for all patients (n = 10). Results are expressed as the mean percent of positive cells ± standard error of the mean.

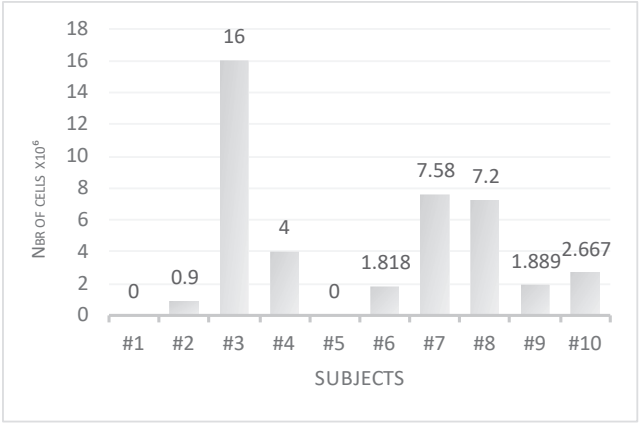

Fig. 7. Mesenchymal stromal cell expansion in primary culture.

obtain between 2.5×10^6 and 8.5×10^6 cells. After 1 year, three out of five patients presented a negative cough-stress-test and two out of five experienced symptom improvement. However, no change in urodynamic-parameters were noticed. Arjmand and colleagues also evaluated SUI treatment with ADSCs in 10 patients over 6 months [16]. The authors transurethrally injected 180,000 cells/ml. They observed a lower ICIQ-SF-score compared to baseline, a significant-decrease in the 24-h pad-test, and a significant-improvement in maximal urethral closing-pressure 6 months after injection. Apart from Kuismanen and colleagues [14] and Arjmand and colleagues [16] each reporting one event of spontaneously resolving postoperative dysuria, autologous ADSC-therapy for SUI has been shown to be safe and well tolerated.

The use of autologous-platelet-concentrates in the field of urogynecology and especially as a treatment for SUI is limited. Their regenerative, anti-infective, and angiogenic-properties make them attractive for tissue repair [22]. Nevertheless, there are only a few case-series studies in the literature [29–31]. According to Matz et al. [29], PRF could theoretically improve multiple urologic conditions, such as erectile-dysfunction, Peyronie's disease and SUI. On average, patients received 2.1 injections of PRF (range:1–8). The PRF was injected into the urethral-submucosa, distal to the bladder-neck, using a cystoscope and resulted in a 50 % decrease in the pad-test. In a recent study, Athanasiou et al. [32] investigated the use of Platelet-rich plasma (PRP) as a treatment option for SUI. In this study, 80 % of women reported improvements after 6 months follow-up. They performed 2 PRP injections into the lower one-third of anterior vaginal wall at 6 week intervals. They concluded that PRP may be an effective treatment for SUI with an excellent safety profil.

This study showed substantial improvement in SUI-symptoms 3 months after implantation, the results were less significant by 9 months post-implantation. Regrettably, there is a lack of scientific evidence demonstrating the long-term efficacy of SVF therapy.

Several mechanisms could be involved in improving the SUI-symptoms of our results. The mechanical impact of fibrosis after the suburethral-dissection could be the cause of the excellent short-term clinical outcomes. Alternatively, the improved continence could be explained by ADSC-induced tissue regeneration. Indeed, the results of the clinical-therapy laboratory show favourable results for the mesenchymal orientation of SVF. In our results, we observed a mean ADSC level of 7.2 ± 2.8 % in the SVF, which is consistent with the research stating that SVF is a heterogeneous population of cells comprised of approximately 1–10 % ADSCs [33]. Unfortunately, the exact mechanism by which SVF injection reduced incontinence couldn't be determined by this preliminary study. Although histological-analysis could determine the exact fate of the injected cells, this invasive-procedure seemed inappropriate in clinical practice. By MRI, We didn't observe a significant increase in suburethral supporting tissue. However, changes in the appearance of the periurethral-tissue were noted with radial densification after the intervention. In 2018, Cui and colleagues assessed the effect of ADSC treatment for SUI in an animal-model [34]. Histological analysis showed that ADSCs could increase the striated and smooth-muscle fibres of the urethra [35].

It is difficult to compare our results with existing literature. Each clinical studies had a different protocol. We injected 0.18×10^6 to $13{,}6 \times 10^6$ fresh SVFs and suburethrally applied SVF/L-PRF. In contrast, the studies cited above used cystoscopy. Because we used a biodegradable material, repeated injections at regular intervals could have improved the long-term results.

The current study does have limitations. It is a preliminary, single-arm, nonrandomized study with a small cohort (n = 10). Outcome was based solely on a validated-questionnaire and a cough-stress test and did not include postoperative urodynamic assessment or 24-h pad-test, which could have supplemented our objective data. Because this procedure is considered as an innovative therapy drug, it is subject to heavy European regulations. Therefore, the balance between cost and benefit should be evaluated in future clinical trials.

Several fundamental points still need to be clarified to validate this cell-therapy. The optimal source of MSCs for tissue regeneration and the optimal number of ADSCs requires further experimental studies. Additionally, the long-term safety profile of ADSC injection must be studied, particularly the theoretical-risk of MSC proliferation. A large-scale controlled clinical trials with rigorous reporting of adverse events is therefore needed. However, based on a systemic review [35] and available clinical trials, no major complications have been observed following ADSC uses.

Conclusion

These preliminary results suggest that the suburethral implantation of a combination of SVF and L-PRF is a feasible and safe modality for treating female SUI. However, evidence is lacking and further research are needed to clarify the respective roles of SVF and L-PRF in female SUI treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research did not receive any specific grant from public, commercial, or non profit funding agencies.

References

[1] Kmietowicz Z. Use mesh implants for stress urinary incontinence only as last resort, says NICE. BMJ 2018;9(363):k4242.
[2] Nguyen A, Guo J, Banyard DA, Fadavi D, Toranto JD, Wirth GA, et al. Stromal vascular fraction: A regenerative reality? Part 1: Current concepts and review of the literature. Journal of Plastic, Reconstructive & Aesthetic Surgery 2016;69(2):170–9.
[3] Squillaro T, Peluso G, Galderisi U. Clinical Trials With Mesenchymal stem Cells: An Update. Cell Transplant 2016;25(5):829–48.
[4] Aufderklamm S, Aicher WK, Amend B, Stenzl A. Stress urinary incontinence and regenerative medicine: is injecting functional cells into the urethra feasible based on current knowledge and future prospects? Curr Opin Urol 2019;29(4):394–9.
[5] Vinarov A, Atala A, Yoo J, Slusarenco R, Zhumataev M, Zhito A, et al. Cell therapy for stress urinary incontinence: Present-day frontiers. J Tissue Eng Regen Med 2018;12(2):e1108–21.
[6] Charbord P, Casteilla L. Human mesenchymal stem cell biology. Med Sci (Paris) 2011;27(3):261–7.
[7] Fu Q, Song X-F, Liao G-L, Deng C-L, Cui L. Myoblasts Differentiated From Adipose-derived Stem Cells to Treat Stress Urinary Incontinence. Urology 2010;75(3):718–23.
[8] Rodriguez LV, Alfonso Z, Zhang R, Leung J, Wu B, Ignarro LJ. Clonogenic multipotent stem cells in human adipose tissue differentiate into functional smooth muscle cells. Proc Natl Acad Sci 2006;103(32):12167–72.
[9] Zhao W, Zhang C, Jin C, Zhang Z, Kong D, Xu W, et al. Periurethral Injection of Autologous Adipose-Derived Stem Cells with Controlled-Release Nerve Growth Factor for the Treatment of Stress Urinary Incontinence in a Rat Model. Eur Urol 2011;59(1):155–63.
[10] Silwal Gautam S, Imamura T, Ishizuka O, Lei Z, Yamagishi T, Yokoyama H, et al. Implantation of Autologous Adipose-Derived Cells Reconstructs Functional Urethral Sphincters in Rabbit Cryoinjured Urethra. Tissue Eng Part A 2014;20(13–14):1971–9.
[11] Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, et al. Human Adipose Tissue Is a Source of Multipotent Stem Cells. Mol Biol Cell 2002;13(12):4279–95.
[12] Yamamoto T, Gotoh M, Kato M, Majima T, Toriyama K, Kamei Y, et al. Periurethral injection of autologous adipose-derived regenerative cells for the treatment of male stress urinary incontinence: Report of three initial cases: Cell therapy for stress incontinence. Int J Urol 2012;19(7):652–9.
[13] Gotoh M, Yamamoto T, Kato M, Majima T, Toriyama K, Kamei Y, et al. Regenerative treatment of male stress urinary incontinence by periurethral injection of autologous adipose-derived regenerative cells: 1-year outcomes in 11 patients: Regenerative therapy of SUI with ADRC. Int J Urol 2014;21(3):294–300.
[14] Kuismanen K, Sartoneva R, Haimi S, Mannerström B, Tomás E, Miettinen S, et al. Autologous Adipose Stem Cells in Treatment of Female Stress Urinary Incontinence: Results of a Pilot Study. Stem Cells Translational Medicine 2014;3(8):936–41.
[15] Choi JY, Kim T-H, Yang JD, Suh JS, Kwon TG. Adipose-Derived Regenerative Cell Injection Therapy for Postprostatectomy Incontinence: A Phase I Clinical Study. Yonsei Med J 2016;57(5):1152–8.
[16] Arjmand B, Safavi M, Heidari R, Aghayan H, Bazargani ST, Dehghani S, et al. Concomitant Transurethral and Transvaginal-Periurethral Injection of Autologous Adipose Derived Stem Cells for Treatment of Female Stress Urinary Incontinence: A Phase one clinical trial. Acta Medica Iranica 2017;55(6):368–74.
[17] Gotoh M, Yamamoto T, Shimizu S, Matsukawa Y, Kato M, Majima T, et al. Treatment of male stress urinary incontinence using autologous adipose-derived regenerative cells: Long-term efficacy and safety. Int J Urol 2019;26(3):400–5.
[18] Aragón IM, Imbroda BH, Lara MF. Cell Therapy Clinical Trials for Stress Urinary Incontinence: Current Status and Perspectives. Int J Med Sci 2018;15(3):195–204.
[19] Van Dijk A, Naaijkens BA, Jurgens WJ, et al. Reduction of infartc size by intravenous injection of uncultured adipose derived stromal cells in a rat model is dependent on the time point application. Stem Cell Res 2011;7(3):219–29.
[20] Jurgens WJ, Kroeze RJ, Zandieh-Doulabi B, et al. One-step surgical procedure for the treatment of osteochondral defects with adipose-derived stem cells in a caprine knee defect: a pilot study. Biores Open Access 2013;2(4):315–25.
[21] Guo J, Nguyen A, Banyard DA, Fadavi D, Toranto JD, Wirth GA, et al. Stromal vascular fraction: A regenerative reality? Part 2: Mechanisms of regenerative action. Journal of Plastic, Reconstructive & Aesthetic Surgery 2016;69(2):180–8.
[22] Nanditha S, Chandrasekaran B, Muthusamy S, Muthu K. Apprising the diverse facets of Platelet rich fibrin in surgery through a systematic review. International Journal of Surgery 2017;46:186–94.
[23] Liu B, Tan X-Y, Liu Y-P, Xu X-F, Li L, Xu H-Y, et al. The Adjuvant Use of Stromal Vascular Fraction and Platelet-Rich Fibrin for Autologous Adipose Tissue Transplantation. Tissue Engineering Part C: Methods 2013;19(1):1–14.
[24] Chen Y, Niu Z, Xue Y, Yuan F, Fu Y, Bai N. Improvement in the repair of defects in maxillofacial soft tissue in irradiated minipigs by a mixture of adipose-derived stem cells and platelet-rich fibrin. Br J Oral Maxillofac Surg 2014;52(8):740–5.
[25] Hajebrahimi S, Nourizadeh D, Hamedani R, Zakaria M. Validity and reliability of the internation- al consultation on incontinence questionnaire-urinary incontinence short form and its correlation with urodynamic findings. Urology Journal 2012;9(4):685–90.
[26] Dohan Ehrenfest DM, Pinto NR, Pereda A, Jiménez P, Corso MD, Kang B-S, et al. The impact of the centrifuge characteristics and centrifugation protocols on the cells, growth factors, and fibrin architecture of a leukocyte- and platelet-rich fibrin (L-PRF) clot and membrane. Platelets 2018;29(2):171–84.
[27] Jurgens WJFM, Oedayrajsingh-Varma MJ, Helder MN, ZandiehDoulabi B, Schouten TE, Kuik DJ, et al. Effect of tissue-harvesting site on yield of stem cells derived from adipose tissue: implications for cell-based therapies. Cell Tissue Res 2008;332(3):415–26.
[28] Andia I, Maffulli N, Burgos-Alonso N. Stromal vascular fraction technologies and clinical applications. Expert Opin Biol Ther 2019;19(12):1289–305.
[29] Matz EL, Pearlman AM, Terlecki RP. Safety and feasibility of platelet rich fibrin matrix injections for treatment of common urologic conditions. Investig Clin Urol 2018;59(1):61–5.
[30] Neto JB. O-Shot :platelets rich plasma in intimate female treatment. J Women's Heal Care 2017;6(5):1–4.
[31] Long CY, Lin KL, Shen CR, et al. A pilot study: effictiveness of local injection of autologous platelet-rich plasma in treating women with stress urinary incontinence. Sci Rep 2021;11(1):1584.
[32] Athanasiou S, Kalantzis C, Zacharakis D, Kathopoulis N, Pontikaki A, Grigoriadis T. The Use of Platelet-rich Plasma as a Novel Nonsurgical Treatment of the Female Stress Urinary Incontinence: A Prospective Pilot Study. Female Pelvic Med Reconstr Surg 2021;27(11):668–72.
[33] Dos-Anjos Vilaboa S, Navarro-Palou M, Llull R. Age influence on stromal vascular fraction cell yield obtained from human lipoaspirates. Cytotherapy Aug 2014;16(8):1092–7.
[34] Cui L, Meng Q, Wen J, Gao Z, Yan Z, Tian Y, et al. A Functional Comparison of Treatment of Intrinsic Sphincter Deficiency with Muscle-Derived and Adipose Tissue-Derived Stem Cells: Effects of MDSCS and ADSCS in the treatment of SUI. IUBMB Life 2018;70(10):976–84.
[35] Lalu MM, McIntyre L, Pugliese C, Fergusson D, Winston BW, Marshall JC, et al. Safety of Cell Therapy with Mesenchymal Stromal Cells (SafeCell): A Systematic Review and Meta-Analysis of Clinical Trials. Beltrami AP, éditeur. PLoS ONE 2012;7(10):e47559.