



A Novel Cell Therapy for Stress Urinary Incontinence, Short-Term Outcome

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Aims: The aim of this study was the safety assessment of urethra injections of autologous total nucleated cells (TNCs) along with platelets, which focused on the outcome over a 6 month period. **Methods:** An open, prospective study was conducted on 9 patients with severe stress urinary incontinence (SUI). At the baseline, 1, 3, and 6 months after external urethral sphincteric and submucosal injections of autologous TNCs along with platelets, the patients were assessed according to cough tests, Q-Tip tests, urodynamics, 1 hr pad tests, upper tract ultrasonography (UTU), post voiding residue (PVR), International Consultation on Incontinence Questionnaire-Urinary incontinence (ICIQ-UI), and International Consultation on Incontinence Modular Questionnaire-Quality of Life (ICIQ-QOL). On the 3rd month post-injection, the maximum urethral closure pressure (MUCP) and abdominal leak point pressure (ALPP) were measured in one patient with intrinsic sphincteric deficiency (ISD; the baseline: ALPP < 60 and MUCP < 30 cmH₂O). **Results:** No complications were observed after injection. At 6-months' follow up (F/U), all the patients considered themselves clinically cured with eight women completely continent and one marked improvement. Mean age was 48.9 ± 13.8 years. Before the injection, urodynamics, UTU, and PVR were normal and cough tests, 1 hr pad tests were positive in patients. At 1, 3, and 6 months post-injection, there was a significant improvement in ICIQ-UI, ICIQ-QOL ($P < 0.05$). UTU and PVR were normal, cough tests, and 1 hr pad tests were negative, except for ISD patient with severe coughs (at month 3: ALPP = 92 and MUCP > 30 cmH₂O). **Conclusion:** Cell therapy consisting of intrasphincteric and submucosal injections of autologous TNCs along with platelets in SUI patients is a feasible and safe procedure. The results point out those subjects cured or with marked improvement after 6 months F/U. *NeuroUrol. Urodynam.* © 2012 Wiley Periodicals, Inc.

Key words: peripheral blood; platelets; stem cells; stress urinary incontinence

INTRODUCTION

Stress urinary incontinence (SUI) is defined as the involuntary leakage of urine on effort, exertion, sneezing or coughing. The well-established risk factors for the development of SUI are pregnancy and vaginal childbirth, vaginal or pelvic surgery, aging, obesity, white race, and smoking.¹ Treatment for SUI includes surgical and non-surgical options. The gold standard treatment option available is an invasive surgical procedure, which uses transvaginal tape (TVT). Ward and Hilton² reported only 63% of the TVT group was objectively cured at 2 years. The subjective cure rate was even less impressive at 43%. Also, adverse events have been reported due to TVT, perforation or laceration of the vessels, nerves, bladder, urethra or bowel during placement, erosion of the vaginal or urethral mucosa or the bladder wall, and fistula development.³

Also, disappointing results were obtained in non-surgical options. Duloxetine is used in pharmacotherapy for treatment of SUI, and is available in Europe, however, it was not approved for use by the FDA.⁴ The use of injectable bulking agents such as polytetrafluoroethylene (PTFE, Teflon), bovine collagen, silicone particles, and carbon beads has yielded short-term success rates in the treatment of SUI. However, such bulking agents cause chronic inflammation and initiate the foreign body giant cell response and other complications associated with the encapsulation of biomedical materials.⁵

"The use of one body part for another or the exchange of parts from one person to another was mentioned in the medical literature even in antiquity and captured the imagination of many over time." (Campbell's Urology 2012, chapter 74 page: 2168).

Abbreviations: SUI, stress urinary incontinence; TNCs, total nucleated cells; F/U, follow up; U/A, urine analysis; U/C, urine culture; ICIQ-UI, International Consultation on Incontinence Modular Questionnaire-Urinary Incontinence; ICIQ-QOL, International Consultation on Incontinence Modular Questionnaire-Quality of Life; ALPP, abdominal leak point pressure; MUCP, maximum urethral closure pressure; UPP, urethral pressure profilometry; ISD, intrinsic sphincteric deficiency; PVR, post voiding residue; UTU, upper tract ultrasonography; ICS, International Continence Society; UFL, uroflowmetry; HES, hydroxyethyl starch; BMSCs, bone marrow-derived mesenchymal stem cells; MDPPSCs, muscle-derived progenitor stem cells; HUCB, human umbilical cord blood stem cell; TVT, transvaginal tape; EPC, endothelial progenitor cells; CEC, circulating endothelial cells; SCP, synergetic cell population.

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Considering the above mentioned treatment options, there is an urgent unmet clinical need in the development of a new minimally invasive approach and effective treatment modality for SUI. Cell therapy for the regeneration of injured tissues has recently been extensively investigated at the experimental level both in vitro and in vivo, and its clinical application in a variety of fields has recently been studied.⁶

There are few reports⁶⁻¹² that use stem cells from different sources used in the treatment of SUI, especially with various success rates in the short-term and long-term outcomes. We report here on the first nine SUI patients included in a larger clinical trial aiming to evaluate the treatment of SUI patients using autologous stem cells and platelets derived from peripheral blood. To the best of our knowledge, this is the first time that this combination of peripheral blood components has been applied in the treatment of SUI.

MATERIAL AND METHODS

Patients

Nine patients with SUI that did not respond to conventional therapy were included in the present study at Imam Reza Academic Hospital from June 2011 until March 2012. The patient's characteristics are presented in Table I.

The study protocol and informed-consent forms were reviewed and approved by the Human Research Ethics Committee of Mashhad University of Medical Sciences. All patients signed the informed consent essential for this study.

Inclusion criteria were: female outpatients, predominant clinical diagnosis of severe SUI, have discrete episodes of incontinence (that are dry between episodes and not continuously leaking urine, synchronous with increased intra-abdominal pressure from coughing, sneezing, and exercising, with mild cystocele (grade 1 and 2 according to POP-Q system) or without cystocele, normal uroflowmetry (UFL), normal pressure/flow cystometry [Normal cystometry considered as normal intravesical pressure (<5–20 cmH₂O) during filling and normal capacity (300–500 cm³) without any uninhibited contracture], normal electromyography (bladder and striated sphincter coordination), which was performed during urodynamic studies and positive cough tests was performed at the beginning of the urodynamic study with a full bladder. For patient with positive cough tests, abdominal leak point pressure (ALPP) tests were performed in order to signify the amount of intra abdominal pressure during leakage. ALPP < 60 cmH₂O and more than 90 cmH₂O has been considered as intrinsic sphincteric deficiency (ISD) and urethral

hypermobility without 1 ISD or with little ISD, respectively. ALPP between 60 and 90 cmH₂O has been considered as equivocal. Urethral pressure profilometry (UPP) was performed in all of the patients. Exclusion criteria were: known vesicoureteral reflux, vaginal prolapse beyond the introitus, or other significant pelvic floor abnormalities, neuromuscular disorder (e.g., muscular dystrophy, multiple sclerosis), uncontrolled diabetes, pregnancy, lactating, or plans to become pregnant during course of the study, morbid obesity (defined as 100 pounds over their ideal body weight, or BMI ≥ 40) and not expected to benefit from treatment, current or acute conditions involving cystitis or urethritis with a history of urogenital cancer scheduled to receive radiation treatment to the vicinity, or history of radiation treatment to the urethra or adjacent structures, current use of any medications for the treatment of urinary incontinence or any mental or physical disability.

At the baseline, the patients were evaluated with cough and Boney tests, Q-Tip test, urodynamic studies, 1 hr pad tests, upper tract ultrasonography (UTU), post voiding residue (PVR), routine laboratory tests, urine analysis (U/A), and culture, the subjective symptoms and quality of life (using a validated disease-specific questionnaire—the International Consultation on Incontinence Questionnaire-Urinary incontinence (ICIQ-UI) and -quality of life (ICIQ-QOL). In the ICIQ-UI was calculated at baseline and repeated 1, 3, and 6 months after treatment. A higher score in the ICIQ-UI and the ICIQ-QOL indicated an unfavorable and a favorable condition, respectively.

The blood was taken 1 day before the injection and 1 g cephazoline was given intravenously 1 hr before the injection. After P-TNCs-M injection, catheter was placed and then was removed the next day to allow maturation, and the patients were discharged with oral antibiotics till 5 days (tablet: ciprofloxacin 500 mg—BID).

Primary outcomes 1, 3, and 6 months after the injection, include cough tests, UTU, UFL, PVR, 1 hr pad tests, ICIQ-UI and ICIQ-QOL were also measured. In one patient with an abdominal leak point less than 60 (demonstrating of intrinsic sphincter deficiency), maximal urethral closure pressure (MUCP) was performed before and 3 months after the operation. In this patient, ALPP was done at 3 months follow up (F/U). The total period of F/U was 6 months.

Platelets and Total Nucleated Cells Separation

One hundred twenty milliliters peripheral blood was taken and total nucleated cells (TNCs) and platelets were prepared

TABLE I. Patient's Characteristics, Past Medical History and Number of Children and Mode of Delivery

No.	Age	Weight	Gravid	Number of children	Mode of delivery	Past medical history
1	61	58	5	5	NVD	—
2	30	90	2	2	NVD	—
3	65	74	13	10	NVD	—
4	55	70	4	3	C/S	—
5	31	68	3	3	NVD	Curettage
6	34	72	4	4	NVD	—
7	61	68	4	4	NVD	—
8	55	64	3	2	NVD	—
9	48	74	5	5	NVD	—
Mean ± SD	48.88 ± 13.8	70.88 ± 8.78	4	4		

NVD, normal spontaneous vaginal delivery, C/S: caesarian.

according to standard procedures. The platelets were prepared by first centrifugation at 2,000g for 2 min and then second centrifugation at 4,000g for 8 min and the supernatant plasma was removed to a final volume of 4 ml.¹³ TNCs were separated and concentrated to 96% purity and to a final volume of about 6 ml using hydroxyethyl starch (HES).¹⁴ HES (HAES-steril 10%; Fresenius Kabi, Germany) was added to the blood to obtain a final concentration of 2%. The blood was allowed to stand for 45 min to allow red blood cells (RBC) sedimentation. The supernatant was slowly separated and centrifuged at 400g for 12 min. After completion of centrifugation, the supernatant plasma was removed to a final volume 6 ml and mixed with 4 ml platelets. The total volume of platelets and TNCs mixture (P-TNCs-M) was 10 ml.

Periurethral Injection of Platelets and Total Nucleated Cells Mixture

The transurethral endoscopic injection of P-TNCs-M was carried out under general anesthesia. A 21-Fr rigid cystoscope was used for injection of P-TNCs-M. The cystoscope was inserted into the urethra. Under endoscopic vision, a puncture needle was passed through the cystoscope into the urethra at the region of the external urethral sphincter. After puncturing the urethra (by a needle with an 18 gauge thickness) at the region of the external urethral sphincter under endoscopic vision, the P-TNCs-M was injected. Initially, 8 ml was injected at a depth of 5 mm into the rhabdosphincter at 1.5, 3, 4.5, 6, 7.5, 9, 10.5, and 12 O'clock positions (1 ml in each position). Subsequently, 2 ml of P-TNCs-M was equally injected into the submucosal spaces at 3 and 9 O'clock positions to facilitate coaptation of the urethral mucosa by the bulking effect.

Statistical Analysis

For the statistical analysis, the GraphPad Instant statistical package was used (GraphPad Software, Inc.). All parameters were given as mean \pm SD. The paired *t* tests and descriptive analysis were employed. The level of statistical significance was set to $P < 0.05$.

RESULTS

There was no morbidity during and after the injection. Mean age of the patients was 48.9 ± 13.8 years. Before the injection, all patients had SUI with positive cough tests and 1 hr pad tests, normal upper urinary tract ultrasonography and normal PVR. Urodynamic findings were normal except for one patient (No. 3) ALPP < 60 cmH₂O and demonstrating of ISD. ALPP were 60–90 (77.66 ± 9.44 cmH₂O) in rest of the patients. The resting UPP was normal in all patients except for patient No. 3. The data on the identification of various cell types before and after process were presented at Table II. The injection took about 10–15 min under general anesthesia.

Eight patients had cured (completely dry) and one patient (patient No. 3 with 13 gravid) had marked improvement according to their ICIQ-UI and ICIQ-QOL. Ultrasonography of the upper urinary tract, PVR and UFL were normal in all patients at 1, 3, and 6 months after, without any evidence of bladder outlet obstruction. Cough test was done at 1, 3, and 6 months in all patients which was negative except for 1 patient (patient 3 with 13 gravid) which was positive in severe cough and ALPP measurement was 92 at 3 month F/U (Table III).

None of the patients had voiding dysfunction, urinary retention or urinary tract infection after P-TNCs-M injection.

TABLE II. The Data on the Identification of Various Cell Types Before Process of Separation and After Process for Final Product

Cell type	TNCs* ($\times 10^8$)	MNCs* ($\times 10^8$)	Platelets($\times 10^{10}$)	RBC depletion %*
Pre-process	7.02 ± 1.18	2.00 ± 0.35	3.46 ± 0.45	NA
Post-process	6.76 ± 1.22	1.88 ± 0.32	3.01 ± 0.11	97.8 ± 1.2
% Yield	96.19 ± 1.92	94.37 ± 1.08	87.95 ± 8.74	

MNCs, mononuclear cells; NA, not applicable.

*Mean \pm SD.

For the patient with ISD (No. 3), baseline MUCP measurement was less than 30 cmH₂O and it was repeated at 3 months F/U, which was more than 30 cmH₂O.

ICIQ-UI base line for patients was 18.33 ± 0.6 and it was reduced to 1.11 ± 0.5 after 1 month. There was significant difference between their scores by paired sample *t* test ($P < 0.001$). At the 3rd and 6th months of F/U ICIQ-UI scores were under one (0.44 ± 0.4). ICIQ-QOL base line for patients was 28.8 ± 3.7 and it was increased to 94.11 ± 12.8 after 1 month. The levels of the ICIQ-QOL was test with repeated measure general linear models and it showed that significant difference among ICIQ-QOL in 1st, 3rd, and 6th months after injection ($P < 0.001$). ICIQ-UI and ICIQ-QOL were presented in Tables III and IV at base line, 1, 3, and 6 months after the operation. There was no recurrence of the symptoms after 6 months.

DISCUSSION

This pilot study shows that the treatment of SUI with mixture of peripheral blood TNCs and platelets is safe and effective method with 8 of patients completely cured and 1 marked with significant improvements 6 months after a single injection.

SUI pathophysiology is caused by weakening of the pelvic floor muscles that support the bladder and urethra (e.g., urethral hypermobility) and/or by weakness of the urethral sphincter (i.e., intrinsic sphincter deficiency [ISD]). Hypermobility occurs when the normal pelvic floor muscles can no longer provide the necessary support to the urethra and bladder neck. As a result, the bladder neck is free to drop when any downward pressure is applied and thus, involuntary leakage occurs. ISD is related to the weakening of the urethral sphincter muscles or the closing mechanism related to contraction. As a result of this weakening, the sphincter does not function normally regardless of the position of the bladder neck or urethra. Cellular aging, cell death (apoptosis and necrosis), and renewal continue throughout life and through all tissues. During aging, apoptosis supersedes renewing capacity which imbalances between cell death and renewal. Therefore, the higher prevalence of SUI among elderly persons is a symptom of increasingly poor and eventually failing tissue regeneration in the vesico-urethral apparatus.¹⁵

Considering the pathophysiology of SUI, the success and efficacy of SUI treatment depends on the reconditioning of phenotypically altered cells, which is augmenting sphincter regeneration. Multipotent stem cells can be differentiated to the myogenic lineage (skeletal and smooth muscle cells), neural and endothelial cell lineages and stem-cell therapy offers a potential cure of the deficient sphincter by regenerating the damaged muscle and connective tissues. Cells transplanted

TABLE III. Outcome of the Patients in 1, 3, and 6 Month Follow-Up

Mode of evaluation	ICIQ-UI			ICIQ-QOL			UTU			Pad test			UFL			PVR			Cough test		
	Baseline	1st	2nd	3rd	Baseline	1st	2nd	3rd	Baseline	1st	3rd	6th	Baseline	1st	3rd	6th	Baseline	1st	3rd	6th	
Patients number																					
1	16	3	0	0	30	88	98	98	N	N	N	N	N	N	N	N	N	N	N	-	
2	21	0	0	0	28	98	100	102	N	N	N	N	N	N	N	N	N	N	N	-	
3	21	4	4	4	24	65	67	65	N	N	N	N	N	N	N	N	N	N	N	+	
4	17	0	0	0	31	108	108	108	N	N	N	N	N	N	N	N	N	N	N	+	
5	16	0	0	0	35	101	101	101	N	N	N	N	N	N	N	N	N	N	N	+	
6	17	0	0	0	24	95	98	98	N	N	N	N	N	N	N	N	N	N	N	+	
7	18	3	0	0	33	99	99	99	N	N	N	N	N	N	N	N	N	N	N	+	
8	20	0	0	0	28	88	95	98	N	N	N	N	N	N	N	N	N	N	N	+	
9	19	0	0	0	27	105	105	110	N	N	N	N	N	N	N	N	N	N	N	+	
Mean ± SD	18.33 ± 0.6	1.11 ± 0.5	0.44 ± 0.4	0.44 ± 0.4	28.8 ± 3.7	94.11 ± 12.8	96.7 ± 11.8	97.6 ± 13													

Normal, N; negative, -; positive, +.

into the urethra can serve as a natural bulking agent and become innervated into the host muscle, potentially improving urethral function.¹⁶

Stem cells have been used from various sources such as bone marrow-derived mesenchymal stem cells (BMSCs), chondrocytes, muscle-derived progenitor stem cells (MDPSCs), adipose derived mesenchymal stem cell, human umbilical cord blood stem cell (HUCB) in preclinical, and clinical studies in order to replenish the lost cells during the tissue regeneration of damaged rhabdosphincter.¹⁷

Corcus et al.¹⁸ showed that the rats BMSCs have the ability to differentiate towards smooth and striated muscle phenotypes, and the periurethral injection of BMSCs significantly improved the injured rhabdosphincter. However, for clinical use, BMSCs is limited due to highly invasive and painful procedures of bone marrow aspiration, a decline in differentiation potential and BMSC number with increased age, and a low yield of BMSCs upon processing and senescence of such cells during culture.¹⁹

The autologous chondrocytes were the first cells type, which used in 32 patients. This treatment was safe, effective, and durable, with 50% of patients remaining completely dry 12 months after a single injection.¹²

In a clinical trial,¹⁰ autologous MDPSCs were injected under transurethral ultrasound guidance into the rhabdosphincter of the mid-urethra. Separate injections of a suspension of autologous fibroblasts, and collagen, which functioned as carrier material, were additionally performed into the submucosa cranial and caudal to the injection side of the MDPSCs with improvements in quality of life and thickness and contractility of the urethral sphincter, with a success rate reported of over 90% for women and over 50% for men.

For eight women, Carr et al.⁹ reported more modest and realistic improvements and changes, with one patient achieving complete continence and four indicating improvement from the baseline 1 year after the initial injection of MDPSCs. Also, a multicentre clinical study showed that intrasphincteric injection of autologous MDPSCs at various doses reduced the amount of leakage during a 24-hr pad tests and lowered the incidence of diary-reported stress leaks over 3 days. These improvements started as early as 1 month after injection and lasted through the study's end point of 6 months, with some evidence suggesting that the higher doses of MDPSCs are associated with greater and faster improvement of incontinence symptoms.¹¹

Adipose-derived stem cells (ADSCs) can express specific striated muscle markers form multinucleated cells characteristic of myotubules, and have been shown to regenerate the functional capacity of damaged skeletal muscle.²⁰ In a two cases study, ADSCs were injected periurethrally in two male patients after radical prostatectomy. SUI improved after 2 weeks of injection and persisted up to 12 weeks after treatment.⁶

In a clinical study, 39 women with incontinence stemming from intrinsic sphincter deficiency, mixed incontinence, or urethral hypermobility; underwent transurethral allogenic HUCBs cell injections. At 12 months after treatment, 72% of patients had more than 50% improvement of their incontinence symptoms.⁷

The ideal cells for tissue engineering should be autologous cells, easily procured from minimally invasive procedures, provide sufficient quantities of cells, exhibit potency of differentiation to regenerate multiple tissues, and proliferate quickly in a well-controlled manner.

In this study, we decided to use the peripheral blood TNCs along with platelets as the first approach of cell therapy for

TABLE IV. The Difference of ICIQ-UI and ICIQ-QOL at Baseline and 1, 3, and 6 Months After Treatment

		P-value			P-value
ICIQ-UI-Base	ICIQ-UI-1mon	0.000	ICIQ-QOL-Base	ICIQ-QOL-1mon	0.000
	ICIQ-UI-3mon	0.000		ICIQ-QOL-3mon	0.000
	ICIQ-UI-6mon	0.000		ICIQ-QOL-6mon	0.000
ICIQ-UI-1mon	ICIQ-UI-Base	0.000	ICIQ-QOL-1mon	ICIQ-QOL-Base	0.000
	ICIQ-UI-3mon	1.000		ICIQ-QOL-3mon	0.332
	ICIQ-UI-6mon	1.000		ICIQ-QOL-6mon	0.194
ICIQ-UI-3mon	ICIQ-UI-Base	0.000	ICIQ-QOL-3mon	ICIQ-QOL-Base	0.000
	ICIQ-UI-1mon	1.000		ICIQ-QOL-1mon	0.332
	ICIQ-UI-6mon	1.000		ICIQ-QOL-6mon	1.000
ICIQ-UI-6mon	ICIQ-UI-Base	0.000	ICIQ-QOL-6mon	ICIQ-QOL-Base	0.000
	ICIQ-UI-1mon	1.000		ICIQ-QOL-1mon	0.194
	ICIQ-UI-3mon	1.000		ICIQ-QOL-3mon	1.000

P-value <0.05 is considered significant difference.

SUI, because of the least invasive method of obtaining the autologous cells such as multipotent cells and endothelial progenitor cells (EPC), which take part in tissue regeneration. Porat et al. found a novel human cell population derived from the peripheral blood, termed synergetic cell population (SCP), which considered as a potential source of autologous treatment for a variety of diseases. The SCP was capable of differentiating into a variety of cell lineages such as angiogenic, neural or myocardial lineages.²¹ Asahara demonstrated the presence of both circulating endothelial cells (CEC) and EPC in peripheral blood.²²

In regeneration medicine, tissue repair is strongly dependent on the formation of new blood vessels and capillaries, which two different processes with cooperation of CECs and EPCs through proliferation, migration and remodeling take place such as vasculogenesis, the in situ assembly of capillaries from undifferentiated endothelial cells (ECs), and angiogenesis, the sprouting of capillaries from pre-existing blood vessels. Angiogenesis is a morphogenic process, which describes the formation of new blood capillaries from EC of pre-existing vessels. When converting to the angiogenic stage, ECs will capture new properties that enable them to neovascularize the tissue. When the new vessels are in place and the vascular network matures, the neovascular ECs resume their quiescent phenotype.³ Angiogenesis has been known for a long time to be essential for muscle repair.⁷ Indeed, endothelial cells (ECs) stimulate myogenic cell growth and, inversely, differentiating myogenic cells to promote angiogenesis.²³

The rationale beyond using the platelets in this study is due to the release of bioactive factors and an extensive documentation of in vitro and in vivo studies demonstrating the safety and efficacy of these factors in the muscle regeneration.²⁴

In platelets, bioactive factors are in the α -granules and the dense granules. In tissue regeneration, the muscle heals through the 3 phases: inflammation, proliferation, and remodeling. These bioactive factors are active during each of these phases. The α -granules contain growth factors such as transforming growth factor- β , platelet-derived growth factor, insulin-like growth factor, fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, and endothelial cell growth factor. These growth factors play important roles in cell proliferation, chemotaxis, cell differentiation, and angiogenesis. The dense granules contain serotonin, histamine, dopamine, calcium, and adenosine. These non-growth factors have fundamental effects on the biologic aspects of tissue repair.²⁵ In general, the bioactive factors play a central role in the healing processes by modulating the recruitment,

duplication, activation, and differentiation of different cell types in muscle repair.

Timothy reported that Cugat (unpublished data) showed an autologous PRP injection directly into the tear in a group of athletes included 8 soccer players and 6 basketball players (accounting for a total of 16 muscular injuries). The return-to-play interval was diminished in each group according to severity, and in the less severe injuries (grades I and II), a greater than 50% reduction in return to play was reported. At regular intervals, F/U included clinical assessment as well as ultrasonic imaging, which confirmed progressive healing of the injured muscle. They concluded that PRP can be helpful in returning athletes to sport, with a shorter time of restoration and rehabilitation.²⁵

LIMITATIONS OF OUR STUDY

In this study, since the mixture of TNCs and PRP were injected, it is not possible to define which one has marked effects on improvement. Future research is needed to distinguish the effects of each of them in detail by choosing different groups of patients. PRP and TNC should be injected separately in two other groups of patients.

Any further conclusions regarding the clinical effects of injections of autologous TNCs along with platelets have to be drawn cautiously due to the limited number of patients. The sample size for the study was calculated to provide us with enough power to demonstrate the differences found in clinical events. Despite this, we believe that the outcome can provide the basis for a larger trial, specifically sized to assess differences in long-term (more than 1 year) clinical outcomes. Another limitation of the study includes the fact we looked this treatment just for patients and as ethical issues we could have a placebo group (injecting normal saline).

In conclusion, the injection of peripheral blood TNCs and platelets is safe and effective in treatment of SIU is a feasible and safe procedure with 6 months F/U. The results point out those subjects cured or marked improvement in 6 months F/U. This study suggests that based on these positive preliminary findings, a larger adequately powered trial is needed to investigate and confirm the efficacy of procedure in long-term outcome.

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A Pilot Study of the Effect of Localized Injections of Autologous Platelet Rich Plasma (PRP) for the Treatment of Female Sexual Dysfunction

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Abstract

Currently, accepted treatments for Female Sexual Dysfunction (FSD) are limited to psychological, behavioral, hormonal and psychopharmacologic interventions. Because of the complex and multifactorial nature of FSD, current therapeutic options may leave a subset of women suffering with sexual dysfunction without clinical improvement. As a simple, safe, and natural alternative therapeutic option for treating female sexual dysfunction, a pilot study was undertaken to test the effect, if any, of vaginal and clitoral injections of autologous Platelet Rich Plasma (PRP) on women desiring treatment for painful intercourse or anorgasmia. Two standardized sexuality tests, the Female Sexual Function Index and the Female Sexual Distress Scale, were administered before and after treatment and were used to measure the response to this therapeutic intervention. Our data indicated some degree of improvement in FSD, including positive changes in isolated sexual difficulties and in the reduction of levels of sexual distress. However, the limited number of participants in this pilot study restricts conclusions. Our initial observations do suggest that further investigation of PRP therapy for the treatment of female sexual dysfunction is indicated.

Keywords: Dyspareunia; Platelet rich plasma; Female sexual dysfunction; Female sexual arousal disorder; Female orgasmic disorder; Hypoactive sexual arousal disorder; Anorgasmia; Injection

Introduction

Because of the many possible etiologic factors involved in female sexual dysfunction and the variability in the response to existing treatment modalities, this area requires research to develop new safe and effective therapeutic alternatives [1]. A recent review of treatment options, when surgically correctable pathology has been ruled out, listed psychological therapeutics and short-term testosterone as the only Level A therapies [1]. A woman with normal hormonal levels or a contraindication to hormonal therapy and no surgical pathology has only psychological therapies as Level A choices for all four classes of sexual dysfunction (i.e. for hyposexual desire disorder, arousal disorder, orgasmic disorder, and dyspareunia) [1]. Although psychological therapies do help many women, there are no other Class A therapeutic alternatives. This indicates that there is a need for further research in this area.

As one possible strategy, a variety of materials have been injected in the periurethral area to treat both sexual dysfunction and urinary incontinence [2]. For example, Calcium Hydroxyapatite Crystals (CHAC) are FDA approved (Coaptite®) for periurethral injection in the treatment of urinary incontinence. However, such therapy may create a discrete constriction that can be associated with urinary obstruction, erosion, infection, and granuloma formation requiring surgical removal [2-6]. With CHAC, no reports show improvement in sexual dysfunction.

Similarly, the injection of hyaluronic acid fillers (the "G-Shot") has been used as a treatment to enhance orgasmic intensity by the amplification of a controversial anatomical area in the anterior vaginal wall (the Graffian Spot). Due to the potential incidence of granuloma formation by hyaluronic acid fillers at the injection site, this therapy has been condemned by the American College of Obstetrics and Gynecology [2-4].

Since investigators have studied the injection of various substances into the vaginal or periurethral areas for treatment of both urinary incontinence and sexual issues, the mechanics and technique of injection into these anatomic sites appears to be safe and well

tolerated. The limiting factor seems to be finding a material that, when injected, produces the desired therapeutic effect without causing untoward side effects.

In contrast to the above mentioned synthetic materials, Platelet Rich Plasma (PRP) has been demonstrated to be effective and without serious side effects in multiple studies in the areas of wound care, orthopedics, dental surgery and in a variety of cosmetic procedures [7-9]. PRP activates pluripotent stem cells in the area of injection, resulting in rejuvenation and even enhancement of damaged or undamaged tissue [10-12]. Moreover, the medical literature contains many articles demonstrating the safety of PRP, with no reports of granuloma formation, infection, or any other serious side effects when FDA approved preparation kits are used [13,14]. Should the PRP be prepared using improperly sterilized tubes, there is the potential for a serious local inflammation or life threatening sepsis. Since PRP is completely autologous, there are no known contraindications to its administration. Technically, PRP injection also offers the advantage of flowing into tissue as a non-viscous liquid and not as a gel (as with hyaluronic acid fillers) or as a particulate slurry (as with calcium hydroxyapatite). The aqueous nature of PRP allows injection through a small bore needle and an even distribution throughout the tissue surrounding the injection site.

Considering the precedent of PRP use in clinical practice, as well as its proven safety, women who presented with complaints of dyspareunia or other symptoms related to sexual dysfunction were offered PRP injections into the periurethral area of the Skenes glands and the clitoris and were observed for their responses to this treatment.

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This pilot study measures the responses of women with varying degrees of sexual dysfunction who received this intervention.

Methods

Eleven females, ages 24-64, presenting with complaints associated with female orgasmic disorder, hypoactive sexual arousal disorder, anorgasmia, or dyspareunia, participated in the study. The patients were seen in clinical private practices and were not paid either to receive the procedure or to complete the survey. All patients were fully informed of the innovative therapeutic and experimental nature of the localized PRP injection and consented to the procedure.

The materials and equipment included the following: (1) 5cc syringes, (2) 27 gauge needles, (3) two separate centrifuges with proprietary collection systems, (4) calcium chloride 10% (for activation of PRP), (5) and a topical anesthetic cream compounded with a base that prevents irritation and promotes absorption through the vaginal mucosa. Active ingredients were as follows: bupivacaine, lidocaine, and tetracaine with percent concentrations of 20/8/8 respectively.

First, a topical anesthetic cream was applied to the anterior vaginal wall. The clitoral hood was retracted and cream applied to the clitoris. Delaying the PRP injection for 20 minutes after anesthetic application achieved complete or near complete analgesia for the procedure. Peripheral blood was drawn from the arm and centrifuged to yield 5 cc of PRP. One of either of two FDA-approved, proprietary collection systems were used according to the standard recommendations for each system: (1) Regen® or (2) TruPRP® [15,16]. Both systems use centrifugation to separate and concentrate PRP. The TruPRP® system concentrates 5 ml of PRP from 60 ml of whole blood using a laser device that visualizes the buffy coat to separate the PRP from RBC's. The Regen® system concentrates 5ml of PRP from 10 ml of whole blood using a gel separator.

After isolation of the PRP, calcium chloride (0.5ml) was added to the 5 ml of PRP isolate to activate the thrombin cascade, thereby causing degranulation of platelets, releasing growth factors and cytokines, and starting the transformation of the PRP to platelet rich fibrin matrix (PRFM) [17]. Before the PRFM became too gelatinous for passing through a needle (less than 10 minutes), two injections were given through a 27-gauge needle, one injection into each of two specific sites: (1) the anterior vaginal wall into a space between vagina and urethra most distal from bladder, and (2) into the clitoris. All authors were trained by Dr. Runels and agreed to perform the procedure in a uniform manner.

Exclusion criteria

Patients presenting with pregnancy, infection, prior genital tract surgery, malignancy or inappropriate affect were not considered eligible for the procedure.

Ethics

This study falls in the category of Medical Practice and Innovative Therapy, which describes an activity that is designed solely to benefit individual patient(s) and does not require IRB review (University of Virginia Institutional Review Board Health Science for Health Science Research).

Data collection

Two standardized tests to monitor the effects of the procedure on sexual function were employed: (1) the standardized Female Sexual Function Index (FSFI) questionnaire and (2) the Female Sexual Distress

Scale Revised (FSDS-R) [18,19]. The FSFI questionnaire measures arousal, desire, pain, orgasm, satisfaction, and lubrication [18]. The FSDS-R questionnaire measures sexually related distress in Females With Sexual Dysfunction (FSD) [19,20]. The FSFI and the FSDS-R were administered before and after the procedure by the patient. Data was obtained at the time of the injection and at 12-16 weeks after receiving treatment.

Previous PRP studies of other tissue types suggests that collection of follow up data at approximately twelve weeks after the procedure allows adequate time to observe therapeutic effects attributed to stem activation and transformation [7-11]. The outcomes measured were the patients' responses to the FSDS-R and FSFI surveys prior to and after receiving the intervention.

Results

Eleven females presenting with dyspareunia (not related to vulvodynia or vaginismus) or with one of the previously mentioned categories of sexual dysfunction, ages 24-64, were included the pilot study group. Of the 11 patients treated, seven (64%) demonstrated some degree of improvement (Table 1). Five of the 7 women who started with elevated levels of sexual distress in the FSDS-R, in which the threshold of distress is defined as a score of 11 or more, dropped their scores to less than 11. Therefore, according to the test criteria, 71% of the women improved from being "distressed" to being "not distressed" after the procedure.

Two patients (18%) showed no change in their levels of distress, but both of these women started with low distress levels. Interestingly, two women (18%), according to their FSDS-R, actually became more distressed after treatment. One of the two who reported more distress subsequent to her PRP injection attributed the worsening of her distress to the loss of her sexual partner. The other woman who reported increased distress explained that after the procedure, her libido increased to a point that it exceeded the ability of her partner to satisfy her.

The mean FSDS-R score dropped 10 points, from 17 to 7 (p=0.04) (Table 2). Nine (82%) of 11 women showed improvement in total FSFI scores. Two (18%) did not experience improvement. The range of improvement in total FSFI scores was from 1.6 to 14.3. The difference between the mean pre-treatment and post-treatment totals was 5.5 (p=0.01) (Table 2). The mean scores for arousal improved by 1.2 (p=0.009), for lubrication improved by 1.28 (p=0.002), for desire 0.82 (p=0.06) and orgasm 1.08 (p=0.05). Since the pre-injection and post-injection scores are observed from the same individual (a repeated-measures design), a paired sample t-test was used, assuming that the

Patient #	PRE-Shot	POST-shot
1	31	2
2	2	2
3	21	35
4	1	2
5	7	4
6	30	4
7	3	3
8	34	14
9	28	0
10	21	7
11	12	7

Table 1: Results for Female Sexual Distress Scale: A score of ≥ 11 effectively discriminates between women with FSD and no FSD.

	Pre PRP Injection		Post PRP Injection*		Difference	95% CI
	n	Mean Score	n	Mean Score		
FSDS-R	11	17.27	11	7.27	0.04	-19.57 to -0.43
FSFI (Total)	11	24.13	11	29.63	0.01	1.48 to 9.52
Desire	11	3.60	11	4.42	0.06	0.03 to 1.67
Arousal	11	3.95	11	5.18	0.009	0.39 to 2.07
Lubrication	11	4.17	11	5.45	0.002	0.57 to 1.99
Orgasm	11	4.11	11	5.19	0.05	0.02 to 2.14
Satisfaction	11	4.04	11	4.40	0.28	-0.35 to 1.08
Pain	11	4.25	11	4.98	0.25	-0.59 to 2.04

*10-16 weeks post treatment **unadjusted

Table 2: Mean scores before and after injection with Plate-Rich Plasma (PRP) of the Female Sexual Distress Scale Revised (FSDS-R) and the Female Sexual Function Index (FSFI). The FSFI individually measures Desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain. The Wilcoxon signed rank sum test was used to assess the difference between the Pre PRP Injection and Post PRP Injection scores.

differences between paired observations are normally distributed. When breaking down the FSFI into the individual domains: desire, arousal, lubrication, and orgasm were significantly increased after injection with PRP. There was no statistically significant effect on satisfaction and pain, although there was a trend toward improvement in those domains.

Side effects

Extreme sexual arousal occurred in 2 patients and included the following: sexual arousal with urination, continuous sexual arousal, ejaculatory orgasm, and spontaneous orgasm. Except for ejaculation, these responses only lasted 1 to 2 weeks and occurred in younger patients who received the procedure with an initial score indicating minimal dysfunction. Other than ejaculatory orgasm, these side effects resolved without further treatment. No other unfavorable side effects were reported.

Discussion

Our results suggest that some cases of female sexual dysfunction, manifested by decreases in sexual desire, arousal, lubrication and orgasmic responsiveness, may be treated with specifically directed injections of autologous Platelet Rich Plasma (PRP) in the area of the Skene's glands and the clitoris. The issue of female sexual dysfunction is quite common. Data shows that sexual difficulties may be experienced by more than 40% of the sexually active adult female population at some time in their lives [21,22]. This percentage represents a sub-set of women who are psychologically distressed by their dysfunction, but do not necessarily consult a physician. Consequently, this statistic may actually be under reported and the condition under-diagnosed because data indicates that only 14% of women may have a conversation with their physician about their sexuality [1]. For sexually dysfunctional women who have not responded to hormonal or psychologic therapies, previous attempts to develop an effective injectable therapy to treat dyspareunia, female orgasmic difficulties, and urinary incontinence have been limited by complications related to the material injected. Autologous PRP injections, on the other hand, have been shown to be safe in other therapeutic areas, since PRP is nonantigenic and contains no synthetic agents that could cause an untoward local or systemic reactions. From our literature search, we could find no reports of granuloma formation, infection, or local tissue necrosis with the use of any of the kits approved by the FDA for preparation of PRP. Since PRP is derived from the patient's own blood, with no foreign or synthetic

substances employed, the body will not react to it immunologically [12]. Hence, there are no reports of allergic reactions to PRP injection.

Studies have demonstrated that PRP induces regrowth of new tissue by of the activation of pluripotent stem cells that are indigenous to most parts of the body. These cells are capable of differentiating into several tissue types, when stimulated by growth factors produced by activated platelets [4-7]. We therefore postulate that when PRP is activated and injected into the anatomic areas involved in sexual responsiveness, growth factors and cytokines may cause differentiation of pluripotent stem cells resulting in neoangiogenesis, fibroblast growth, glandular proliferation (Skene's glands), and new neuronal growth—resulting in improved physiologic responsiveness. Improved vascularity and neuronal regrowth in the vagina and in the clitoral area could restore or possibly enhance sexual responsiveness and sensitivity by increasing blood flow to the area, especially in cases where hormonally independent vaginal atrophy contributes to FSD. In addition to increased blood flow, collagen and sensory nerve regrowth might relieve coital discomfort as well as enhance vaginal sensitivity. Also, increased blood flow in the clitoris, if induced by PRP injections, could also lead to improved arousal and orgasm.

The extreme sexual arousal observed in two of our patients may have resulted from a volumetric effect of the PRP injection, causing continuous pressure on the urethra and the Skene's glands. This effect can result from Platelet Rich Fibrin Matrix (PRFM), in which the PRP interacts with thrombin to form a matrix. If Platelet Rich Fibrin Matrix in the periurethral tissue behaves as it does in the dermis of the arm, then this matrix would resolve within 2 weeks to become replaced over the following 8 weeks with new tissue growth [12].

There are certain obvious limitations to this study. Because of the small number of patients in this pilot study, the statistical power of this study is limited and, as such, only suggests a possible effect of our intervention. Furthermore, due to the complexity of the female sexual response and the importance of emotional factors in sexual responsiveness, a placebo effect must be considered when evaluating our findings. Another possible limitation of our pilot study is its observational and subjective nature, despite the use of standardized diagnostic questionnaires. Despite the potential methodologic problems inherent in a pilot study involving female sexuality, because of the patient's positive response to our intervention, without the incidence of complications, future prospective, placebo controlled studies are planned.

Conclusions

The preliminary results of this pilot study suggests that specifically placed intravaginal and intraclitoral PRP injections could be an effective method to treat certain types of female sexual dysfunction, especially in the areas of desire, arousal, lubrication and orgasm. Improvement in satisfaction and pain were noted, but were not statistically significant.

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