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Original Article

The Effect of Periurethral Injection of Pure Platelet-rich Plasma in the Treatment of Urinary Incontinence in Female Patients: a randomized clinical trial

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ABSTRACT

Background: Stress urinary incontinence is a prevalent condition among a large number of women and has a negative effect on their quality of life. One treatment option is the use of bio-injectable materials to enhance closing pressures. In this study, we aimed to investigate the effects of the periurethral injection of pure platelet-rich plasma on the treatment of stress urinary incontinence.

Methods: This study was conducted as a randomized controlled clinical trial on 20 women with stress urinary incontinence. Ten patients received periurethral injections of pure platelet-rich plasma (experimental group), while ten patients received midurethral sling procedure as the standard treatment for stress urinary incontinence ((control group). Follow-up was performed one and three months after the treatment using the international consultation on incontinence questionnaire (ICIQ), incontinence quality of life (I-QOL) questionnaire, urogenital distress inventory (UDI-6), and cough stress test.

Results: Out of ten patients in the experimental group, seven cases (70%) relatively recovered after the injection. Out of ten patients in the control group, eight patients completely recovered after the procedure. There was significant difference in the questionnaire results before and after treatments, which indicates the effectiveness of these treatments in both groups. However, the response to the midurethral sling procedure was better than the response to pure platelet-rich plasma injection, and the difference was statistically significant.

Conclusion: The periurethral injection of a single dose of pure platelet-rich plasma could relatively eliminate the symptoms of stress urinary incontinence in patients. More definite results can be obtained with repeated doses of pure platelet-rich plasma, even compared with standard treatments.

Keywords: Stress urinary incontinence, Platelet-rich plasma, Midurethral sling

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Introduction

According to the International Continence Society, stress urinary incontinence (SUI) is defined as a complaint of urinary incontinence due to abdominal pressure, such as exercise, laughter, sneezing, and coughing (1, 2). Conservative and surgical treatments are among the conventional methods used to treat urinary incontinence. The conservative therapies include pelvic floor physiotherapy, biofeedback, electrical stimulation, and continence devices (3, 4). On the other hand, the surgical techniques used to treat SUI include Burch colposuspension, suburethral slings, bladder neck injection, and artificial urinary sphincter insertion.

Among surgical procedures, midurethral sling is a common and standard method for treating urinary incontinence in women (5). Although surgical techniques offer long-term treatments for SUI, they are not complication-free. Surgical techniques may cause various complications, such as bleeding, bladder trauma, and urinary tract trauma, during the surgery or lead to delayed complications, such as pain, infection, urinary retention, bladder and urethral perforation, and vaginal erosion and extrusion (6). One alternative procedure to sling surgery is the injection of urethral bulking agents (UBAs) due to its lower invasiveness (7, 8). However, due to their limited durability and efficacy, these interventions have mainly lost their clinical value (9).

The use of stem cells and other progenitor cells as injectable agents, offers potential alternative therapies. Another effective method for the treatment of SUI is the combined use of injectable autologous compounds, which reconstructs the structure and function of ligaments surrounding the urethra and reduces surgical complications and high cost of stem cell application (10, 11). Many researchers have examined the reconstruction potential of blood components and plasma derivatives and proposed the use of autologous compounds (11), including fibrin adhesive and platelet derivatives, such as platelet-rich plasma (PRP) and platelet-poor fraction (PPF) in low-cost tissue repair (5).

Generally, granules inside platelets contain substances that are involved in a cascade process and promote the production of several growth factors and cytokines (12, 13). Today, PRP is recognized as the most studied platelet derivative (14). Naturally, 6% of the human blood is composed of platelets. However, PRP contains a significant concentration of platelets. Effective clinical results can be obtained by using PRP with a platelet concentration two to four times higher than that of healthy blood. Moreover, as a carrier of various growth factors (e.g., IGF-1, TGF-β, VEGF, PDGF, HGF, and FGF) and cytokines (e.g., IL-1, IL-6, and IL-8), PRP stimulates angiogenesis, endothelial cell migration, cell division, regulation of protein production, stimulation of collagen synthesis, and extracellular matrix production, which in turn accelerate the repair of ligaments and tendons (15-18).

Although PRP has been applied in the past 30 years in many areas, such as orthopedics, cosmetics, medicine, sports, jaw and facial treatments, and urology, it has not been used independently in the treatment of SUI among women.

With this background in mind, the present study aimed to compare the efficacy of two less invasive treatments for stress urinary incontinence being periurethral injection of PRP and mid urethral sling as a pilot study.

Materials and Methods

This prospective randomized controlled clinical trial was performed on women aged 30-65 years diagnosed with SUI and referred to the urology clinic of Kerman University of Medical Sciences, Kerman, Iran in 2018 (IRCT20171201037697N1). The participants had not responded to conservative therapy or medication therapy and were proper candidates for the study according to the study criteria. The draft of the research project was reviewed and approved by the Ethics Committee of Kerman University of Medical Sciences. After entering the study, the subjects were first informed about the study methods, aims, advantages, and disadvantages. Those who were willing to take part in the study completed a written consent form.

The inclusion criteria were as follows: 1) Female patient with primary symptoms of SUI confirmed by patient's medical history and clinical symptoms, including a focused incontinence evaluation; 2) age range of 30-65 years; and 3) patient's willingness to undergo surgical treatment. On the other hand, the exclusion criteria were as follows: 1) residual urine volume exceeding 100 cc after excretion; 2) evidence of detrusor over-activity on the urodynamic test; 3) history of suburethral sling

procedure or other urogenital surgeries; 4) active urinary tract or vaginal infection; 5) malignancies of the genitourinary system; 6) history of hemorrhagic disorders; 7) recent history of genitourinary fistula or urethral diverticulum; 8) advanced pelvic organ prolapse on the pelvic examination; 9) uncontrolled diabetes mellitus, and 10) any other contraindications for surgical procedures.

Since the present study was the first research in this area on human samples, the sample size was estimated at 20 people. The participants were categorized into the experimental and control groups (10 per group) according to the table of random numbers considering the time of referral and the inclusion criteria. The patients were evaluated subjectively using the international consultation on incontinence questionnaire (ICIQ), urogenital distress inventory questionnaire (UDI-6), incontinence quality of life questionnaire (I-QOL), and objectively using cough stress test.

In the experimental group, after blood transfusion and PRP preparation, cefazolin (1 g) was intravenously injected, and periurethral injection was performed after one hour. The patients were discharged after ensuring their full recovery and stable clinical condition. The patients in the control group received a standard midurethral sling treatment. The patients' responses to the treatments were evaluated one and three months after the treatments, using UDI, ICIQ, and I-QOL questionnaires, and cough stress test. Three of patients in the experimental group were willing to receive the subsequent dose. The second injection was given one month subsequent to the first injection, and in one case, a third injection was performed one month after the second injection.

PRP preparation method

Venous blood (20 mL) was stored using acid citrate dextrose (ACD) anticoagulant, and falcon tubes (15 mL) were centrifuged for 10 minutes at 800 rpm. After separation of PRP, which was deposited on red blood cells, it was transferred into new 15-mL falcon tubes. They were then centrifuged for 15 minutes at 3500 rpm, and platelet concentrates were prepared by removing the platelet-poor plasma supernatant.

PRP injection method

Approximately 3 mL of the platelet concentrate was injected via cystourethroscopy at four points in the middle of the urethra with endoscopic needles under regional anesthesia. Injections were performed by a urologist in the operating room of the hospital.

Data analysis

In this study, mean and standard deviation were measured to determine the data distribution. Paired t-test was also employed to analyze the data before and after the treatments considering the normal distribution of data. Moreover, an independent t-test was employed to compare the results of the experimental and control groups. Chi-square test was also applied for qualitative variables. SPSS version 19 was employed for statistical analysis, and the significance level was set at $P<0.05$.

Results

1. Comparison of age and parity

The mean age of the subjects was 50.9±2.76 years in the experimental group (treated with PRP) and 45.7±1.99 years in the control group (treated with the midurethral sling procedure). In addition, the mean parity was 4.4±0.76 in the experimental group and 3.4±0.34 in the control group. No significant difference was observed between the groups in terms of these variables (Table 1).

Table 1. Evaluation and comparison of age and parity in the groups

	PRP injection		Midurethral sling procedure		P-value
	Mean	Standard deviation	Mean	Standard deviation	
Age	50.90	8.74	45.70	6.30	0.37
Parity	4.40	2.41	3.40	1.17	0.37

2. Comparison of cough stress test results

In both groups, all patients tested were positive for the cough stress test. In the group treated with PRP, one month after the treatment, the cough stress test results were positive for three patients and negative for the rest (n=7). In the control group, the results were positive in two patients and negative in the rest (n=8) (Table

2). The present findings showed that in both groups, the cough stress test results were not significantly different between the one-month and three-month follow-ups.

Table 2. Evaluation and comparison of cough stress test results in patients

		PRP Injection N (%)	Midurethral sling procedure N (%)	*P*-valu
Before treatment	Positive	10(100)	10(100)	
	Negative	0(0)	0(0)	-
three months after treatment	Positive	3(30)	2(20)	0.45
	Negative	7(70)	8(80)	

3. Comparison of ICIQ, UDI-6 and IQOL questionnaires results

In the group treated with PRP, the mean scores of ICIQ before, one month and three months after the treatment were 17.85±1.98, 7.90±4.94, and 8.0±6.8, respectively. The difference of before and after the treatment was statistically significant (P<0.002) indicating the effect of this method in the treatment of SUI. Moreover, in the group treated with the midurethral sling procedure, the mean scores before the procedure, one month and three months after the procedure were 17.9±1.66, 2.2±3.4, and 2.2±3.5, respectively. The results showed that response to this treatment method was statistically significant (P<0.001). In both groups, no significant difference was observed between the mean scores of one and three months after the treatment (p=0.2). Moreover, no significant difference was observed between the two groups in the mean score of ICIQ before the treatment. Nevertheless, in both evaluations of one and three months after the treatment, the effectiveness of sling treatment was higher than that of PRP treatment, and the difference was statistically significant (Table 3).

Table 3. Evaluation and comparison of ICIQ and IQOL results in the two groups [International consultation on incontinence questionnaire (ICIQ), Incontinence quality of life questionnaire (I-QOL)]

		PRP injection (N=10) Mean (SD)	Midurethral sling procedure (N=10) Mean (SD)	*P*-value
ICIQ	Before treatment	17.8(1.98)	17.9(1.63)	0.9
	One month after treatment	7.90(4.94)	2.20(3.4)	0.008
	Three months after treatment	8.0(6.8)	2.2(3.5)	0.02
I-QOL	Before treatment	43.9(10.87)	42.6(5.24)	0.7
	One month after treatment	80.6(28.47)	105.3(7.42)	0.01
	Three months after treatment	75.4(23.91)	104.8(7.61)	0.01

The mean scores of I-QOL before the treatment and one month after the treatment were 43.9±10.87 and 75.4±23.97 in the PRP group and 42.6±5.24 and 105.3±7.42 in the midurethral sling group, respectively, indicating a significant increase in the quality of life in both groups (P<0.01). No significant difference was observed between the two groups in the mean score of I-QOL before the treatment. However, the increase in the mean score was significantly higher in the midurethral sling group one month after the treatment, compared with the PRP group. The mean score of I-QOL in the experimental group decreased from 80.6(28.47) to 75.4(23.91) after three months. However, in the control group, the mean score did not indicate any significant difference three months after the treatment (Table 3).

In the experimental group, the mean scores of UDI before the treatment and one month after the treatment were 11.70±2.54 and 6.1±3.6, respectively. In the control group, the mean scores of UDI were 10.3±1.88 and 1.3±1.7 before and one month after the treatment, respectively. The difference in the scores before the treatment and one month after the treatment indicated the significant response of both groups to the treatment (P<0.01).

In comparison of the control and experimental groups one month after the treatment, the total score was significantly higher in the experimental group. Accordingly, response to the surgical treatment in the control group was significantly greater than that in the experimental group receiving PRP treatment (Table 4).

Table 4. Evaluation and comparison of UDI-6 questionnaire results in the two group (Urogenital distress inventory questionnaire (UDI-6))

	PRP injection	Midurethral sling procedure	*P*-value
	Mean (SD)	Mean (SD)	
QUDI			
Before treatment	11.70 (2.54)	10.3 (1.88)	0.1
One month After treatment	6.1 (3.6)	1.30 (1.7)	0.001
Three months after treatment	6.6 (5.7)	1.3 (1.7)	0.007

The mean score of UDI in the experimental group increased from 6.1(3.6) to 6.6 (5.7) three months after the treatment. However, the mean score of the control group was not significantly different after three months compared with that in the one-month follow-up.

5. Results of subsequent PRP injections

The second injection of PRP was performed in three patients (one month after the first injection), and one patient received the third injection (one month after the second injection). However, statistical analysis was not possible because of the limited number of these patients. Therefore, the results of the second and third stages of treatment are presented below as raw data (Table 5). The first patient showed relative recovery after the first injection; nonetheless, the symptoms recurred after the second injection.

The response of the second patient to the treatment was excellent after the second and third injections, and the cough stress test result was negative. The patient was completely satisfied with the treatment. The response of the third patient to the treatment after the second injection was significant and superior to the first injection. In addition, the patient was satisfied with the treatment, and the cough stress test result was negative.

Table 5. Treatment results in three patients receiving the second and third injections of PRP

	Cough test				UDI				I-QOL				ICIQ			
Number of injections	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Patient 1	+	+	+		14	7	12		45	70	52		15	8	14	
Patient 2	+	-	-	-	8	2	0	0	65	98	109	110	21	4	0	0
Patient 3	+	-	-		12	6	3		40	86	108		18	7	2	

6. Complications in the two groups

The patients did not report any complaints or complications related to the treatments.

Discussion

SUI is one of the common complaints of patients, especially women, with negative effects on their quality of life, mental health, and social functioning. In terms of SUI treatment, surgery is presently considered as the most efficacious option, and midurethral sling is the standard procedure (19, 20). Nonetheless, the invasiveness of surgery and the risk of synthetic mesh are the drawbacks of this procedure (19, 20). In addition, a negative attitude has been established towards procedures involving these sorts of materials (21); therefore, a large number of SUI patients decline to consider the midurethral synthetic sling procedure. On the other hand, some patients are unable to go through a complex laparoscopic surgery for urinary incontinence owing to medical comorbidities. Therefore, it is absolutely crucial to find an efficacious and minimally invasive treatment.

The pathophysiology of SUI involves urethral hypermobility and intrinsic sphincter deficiency (ISD); one of the important causes of ISD is the loss of balance between cell death (apoptosis) and cell regeneration, during which cell death increases and regeneration decreases. Over the past few years, cell therapies have been investigated using the injection of musculoskeletal stem cells, adipose tissues, fibroblasts, cord blood, and platelets (e.g., PRP and PPP). Autologous stem cells can be injected into the urethral sphincter with the goal of regenerating deficient anatomical components of the urethra in the urethral continence mechanism. Moreover, stem cell therapy has the potential to restore the external and internal urethral sphincters, neuromuscular synapse, and blood supply (22). Considering its mechanism, this therapy is considered as the most efficacious treatment for ISD patients. The advantages of cell-based therapy for SUI include treatment of the cause rather than merely the symptoms and

lack of immunologic response with the use of autologous cells. Also, biopsy and urethral injection can be performed under local anesthesia.

Although researchers have examined the treatment of SUI by muscle-derived stem cells (MDSCs), bone marrow, umbilical cord, and adipose tissues, a small number of studies have assessed the impact of PRP on SUI (23). In this regard, in a study conducted by Kleinert et al. (2008) on 63 women with SUI, 42 patients received treatment with transurethral injections of autologous myoblasts and fibroblasts under guided sonography, while 21 patients were candidates for several collagen injections. After 12 months of follow-up, 38 out of 42 patients fully recovered (24).

Moreover, in a study conducted by Peter et al. (2014) on the effectiveness of MDSCs in repairing urethral sphincters, 80 women with SUI were treated with different doses in several groups. In the 12-month follow-up, patients who had received higher doses showed more than 50% reduction in urinary leakage due to stress (25). Also, in a systematic review which was conducted in Poland by Pokrywczynska et al. (2015), sixteen papers on the effect of cell-based therapy for SUI were reviewed. According to the results, the treatment of 616 male and female patients was associated with the mean full recovery rate of 37.2% and the mean relative recovery rate of 29.7% (26).

PRP triggers the regeneration process by forming growth factors and cytokines and promotes SUI treatment. Therefore, PRP may offer a minimally invasive and effective therapeutic alternative to surgery. Furthermore, compared with stem cells, PRP can be easily prepared and is relatively inexpensive. In the present study, we evaluated the effect of the periurethral injection of PRP on the treatment of SUI. This pilot study was conducted as a randomized controlled clinical trial on 20 women with SUI. Ten patients received periurethral injections of PRP in the experimental group, while ten patients received standard treatment for SUI (midurethral sling procedure). According to the findings, 70% of patients recovered relatively after the injection, while 30% showed almost no response. Two out of three patients, who had received subsequent doses of PRP, fully recovered. Eight out of ten patients, who had been treated with the midurethral sling procedure, fully recovered, while no response to the treatment was observed in two patients.

In this regard, a study by Behnia et al. demonstrated the short-term and long-term impacts of transvaginal PRP injection and laser therapy on SUI. The participants stated that their SUI symptoms had improved within three and 12-24 months after the treatment, and significant changes in the symptoms were observed, compared with the pre-treatment stage. They suggested that the combined use of PRP and fractional microablative CO_2 laser might be an efficacious treatment for SUI (27). However, since they did not compare the results of patients receiving PRP and laser therapy, the results did not indicate the effects of PRP or laser therapy on the improvement of SUI. Furthermore, they did not compare the results with other standard treatments or a control group. Amirzargar *et al.* also showed that PRP and fat might be used to treat women with SUI. Their results were promising considering the different aspects of their study, such as the intensity of urinary incontinence based on the questionnaire, changes in fat tissue thickness based on MRI, and level of abdominal leak point pressure based on the urodynamic study (28).

Moreover, in a study conducted in Mashhad, Iran, Shirvan et al. (2013) investigated the effects of simultaneous injection of total nucleated cells (TNCs) and PRP on SUI in nine patients. According to their results, eight patients showed full recovery after six months, and one patient experienced a significant recovery. The mean scores of ICIQ in these patients were 18.33, 1.11, and 0.44 before, one month, and three and six months after the treatment, respectively. Furthermore, the mean scores of I-QOL were 28.8, 94.11, 96.7, and 97.96 before, one month, three months, and six months after the treatment, respectively (29).

According to the findings of the present study, the periurethral injection of a single dose of PRP can result in a relative recovery of patients with SUI. Although the effectiveness of this method was lower than the standard midurethral sling procedure, the administration of the second and third dosages of PRP resulted in the full recovery of two patients. However, we could not collect sufficient data in this area, as other patients were not willing to receive the subsequent doses of PRP. This study had some limitations; the sample size was limited and follow-up of our patients was short-term. In order to clarify the number of injections needed

to maintain the effect of periurethral PRP injection, longer follow-up studies with more injections are requierd. It is suggested to perform the second phase of this study on a larger sample for a longer follow-up period with several PRP injections.

Conclusion

In the present study, the periurethral injection of a single dose of PRP could relatively eliminate the symptoms of SUI. However, the effectiveness of this method was significantly lower than the standard midurethral sling procedure. Since PRP can be prepared easily, is comparatively economical, and can be safely administered, further research is required to examine this potential therapeutic strategy for SUI.

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