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### Platelets Rich Plasma Injections in The Treatment for Stress Urinary Incontinence in Postmenopausal Women

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#### Abstract

Stress urinary incontinence is the most common type of UI in women and defined as in voluntary loss of urine on effort, physical exertion, or on sneezing or coughing. It is considered one of the most common dysfunctions of the lower urinary tract and represents a worldwide problem affecting people of all ages and across different cultures and races. Platelet-rich plasma (PRP) is becoming more common as a non-operative therapy choice for a wide spectrum of medicinal disturbances including stress urinary incontinence. To assess the efficacy and feasibility of platelet rich plasma injections in the treatment of stress urinary incontinence in postmenopausal women. Patients and Methods: Prospective randomized clinical study was conducted at the Department of Obstetrics and Gynecology, Al-Zahra University Hospital between June 2020 and June 2021 on selected thirty postmenopausal women with complaint of stress urinary incontinence. All thirty women had received a treatment with Platelet Rich Plasma injections in pubocervical fascia by specialized technique in one session and the 2nd injection was done when the patient need after two months. In this study the improvement in stress urinary incontinence after1st injection of PRP was in 11 cases with percentage of 36.7 % of cases in addition to complete cure of 8 cases with percentage of 26.7 % of cases. After two injections of PRP, complete cure of 14 cases, improvement in degree of severity in 11 cases and only 5 cases not improved in grade of severity of incontinence with percentage of 16.7 % of the cases. Local injection of autologous platelet rich plasma has a curative effect on females suffering from stress urinary incontinence with high efficacy and success rate.

Keywords: Stress incontinence, Platelet rich plasma, Urinary incontinence.

#### 1. Introduction

Stress urinary incontinence (SUI) is one of the main health issues, which influence almost about 20% of mature females and has a harmful effect on their daily performances and quality of life, with older women more likely to be affected. It is either due to intrinsic sphincter deficiency (ISD) or urethral support defect

(hypermobility) [1]. For most patients, the beginning administration of simple SUI various non-invasive involves behavioral interferences. involving amendments, Pelvic floor exercises (PFEs) with or without biofeedback and another educational support [2]. Many operative approaches have been suggested to the therapy of Stress urinary incontinence. Between them are Burch Colposusspension, autologous fascia bonds, retropubic midurethral sling MUS, transobturator tapes (TOT), trans-obturator tapes inside out (TOT-O), bladder neck synthetic injections and urethral sphincters, are more usually applied [3]. Another alternative technique for the remediation of stress urinary incontinence, the use of an injectable factor which could mostly regain the PUL's structure and function. This renewable base of autologous materials could possibly limit the side effects of artificial substances. Interestingly, although the prevalent utilization of fibrin cohesive and plateletrich plasma in different areas over the previous thirty years, these materials have not been utilized for the therapy of women Stress urinary incontinence [4]. This therapy modality is derived from natural recovery steps, like the body's first echo of tissue damage is to deliver platelets to the region. Platelets damaged improve recovery and catch stem cells to the region of the damage. Moving from basic science to clinical practice, PRP injections have been used to treat diseased nexuses, sinews, and joints, with super findings in terms of repair [5]. Previous studies examining the rejuvenate capabilities of plasma (platelet-rich or platelet poor fragments) offer chances of utilizing an autologous materials with slimy, treating, and hemostatic properties at a minimal cost injecting an autologous sticky agent to the PUL, might have favorable outcomes in the remediation of the Stress urinary incontinence via re-approximating the urethra and the bladder neck to the pubic bone, a technique which could repaired

urethral hypermobility, regain the normal anatomy in the area with lower pains [6]. Various platelet derived fragments have been characterized. Between them, pure platelet-rich plasma (PRP) is the greatest commonly studied in tissue regeneration. PRP includes various growth agents that are attributed to the pathophysiology of ligament rebuilding involving vascular endothelial growth factor (VEGF), insulin growth factor I (IGF-I), platelet derived growth factor (PDGF), hepatocyte growth factor (HGF), transforming growth factor beta (TGF-b) and fibroblast growth factor. (FGF) [7]. Aim of the work assesses the efficacy and feasibility of platelet rich plasma injections in the treatment of stress urinary incontinence in postmenopausal women.

#### 2. Patients and Methods

This prospective randomized clinical study was conducted at the Department of Obstetrics and Gynecology, Al-Zahra University Hospital between June 2020 and June 2021. On selected thirty (30) postmenopausal women with complaint of stress urinary incontinence, fulfilling the inclusion and exclusion criteria.

## 2.1 Inclusion criteria of the participants:

Including postmenopausal women with complaint of stress urinary incontinence.

#### 2.2 Exclusion criteria:

Chronic renal failure, Chronic diabetes mellitus, Urinary tract infection, Hysterectomy, Neurological diseases as multiple sclerosis, Genital prolapse.

#### 2.3 Methodology:

After ethical approval of the study protocol by the Ethics Committee Faculty of Medicine Al-Azhar University (No. of approval: 2021121135), Informed consent

from all patients was taken. Full history taking, complete general, abdominal pelvic and neurological examinations were done. Also, Q tip test and stress test were done in Urodynamic study test to addition to diagnosis confirm of stress the incontinence. All cases had answered a questionnaire (ICIQ) indicating symptoms of stress incontinence before and after treatment, showing the grade of the disease and the degree of improvement after treatment. All baseline investigations including complete blood count, random blood sugar, kidney function tests, liver function test were carried out. All those thirty women had received a treatment with a Platelet Rich Plasma injection in by pubocervical fascia specialized technique in one session and the 2nd injection was done if the patient need after two months. Patients' reassessment was done every two weeks after first injection by patient symptom. Patient complains and symptoms of side effects like pain, dysuria, worsening of SUI was observed. Failure of the treatment was considered if there were no improvement after one month from the second injection or there were serious side effects as worsening of SUI.

#### 2.4 Technique of PRP injection

Peripheral blood had been dragged from anesthetic the arm and an cream benzocaine 20%; Lidocaine 6%: Tetracaine 4% utilized in the vulvo vaginal region. The kit was equipped with a butterfly 23G needle, Vacutainer Kit, 10% calcium chloride, 5cc syringe and 30 1/2 needle. 4cc blood samples were inhaled from the participating's peripheral vein in a vacuum gathering tube with separator gel, which is centrifuged separating red and white cells at 3.100RPM for nine minutes. Platelet cells were on top of the tube and the 2cc of cell suspension are known as PRP. Following the isolation of the PRP, 10% of CaCl2 0.1cc was added to 2cc of platelet rich plasma and injected using a 5cc syringe with 30G <sup>1</sup>/<sub>2</sub> needles in Pubocervical fascia.





# 2.5 Method of data management and statistical analysis

Results were entered into the computer and analyzed utilizing the IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative results have been expressed by utilizing numbers and percentages. Quantitative results have been expressed utilizing range (min and max), mean, standard deviation, median, and interquartile range (IQR). The significance of the data was assessed at a 5% level. The utilized tests were the Chi-square test for categorical variables, to compare between various groups; Monte Carlo correction for correction for chi-square when > 20% of the cells have an expected count < 5, and the F-test (ANOVA), for normally quantitative distributed variables. to compare between more than two groups. For abnormally distributed quantitative data, the Kruskal-Wallis test is used to compare more than two groups.

#### 3. Results

Table .1 clears the distribution of the examined patients regarding age with minimum age was 47 years and maximum

was 67 years with mean of age in the cases  $54.80 \pm 6.01$  years.

There was statistically significant positive correlation between degree of severity of stress incontinence and age as shown in Figure. 1.

Table. 2 shows distribution of studied cases according to parity with all cases were multipara ranged from P2 to P7 with mean of parity in the cases  $3.57 \pm 1.22$ .

There was no statistically significant correlation between degree of severity of stress incontinence and parity as shown in Figure. 2.

Table. 3 shows that mode of delivery was normal vaginal delivery in 25 cases with percentage of 83.3 % of the studied cases and cesarean section delivery in 5 cases with percentage of 16.7 % of the studied cases.

Table. 4 shows distribution of cases according to period of menopause in years with mean of  $6.53 \pm 4.14$  years. Minimum period was one year, and maximum was 17 years.

There was statistically significant positive correlation between degree of severity of stress incontinence and menopause as shown in Figure. 4. Table. 5 shows that mean BMI of the 30 studied cases was  $30.17 \pm 4.94$  kg/m2 with minimum BMI 23.0 kg/m2 and maximum was 41.50 kg/m2.

There was no statistically significant correlation between stress incontinence and BMI as shown in Figure. 5.

Table. 6 shows classification of cases according to degree of severity of stress urinary incontinence measured by ICIQ score. 3 cases were mild with percentage of 10 % of cases, 15 cases were moderate with percentage of 50 % of cases and 12 were severe with percentage of 40 % of cases.

Table. 7 shows classification of cases according to degree of severity of stress incontinence measured by ICIQ score post treatment with platelet rich plasma (PRP) injection. The table shows movement of disease cruelty distribution to moderate diseases following PRP injection as follow: complete cure of 8 cases after first injection, 3 cases mild, 16 cases moderate and 3 cases severe. After  $2^{nd}$  injection of non-cured cases (n = 22) 6 cases had completely cured, 4 cases mild, 10 cases moderate and 2 cases still severe.

Age (years)	No.	%	
<50	7	23.3	
50 - 60	18	60.0	
>60	5	16.7	
Min. – Max.	47.0 -	- 67.0	
Mean ± SD.	$54.80\pm 6.01$		
Median (IOR)	53.50 (49.75 - 58.50)		

**Table (1):**Distribution of the examined patients regarding age.

**Table (2):** Distribution of the examined patients regarding parity.

Obstetric history	No.	%	
Parity $(n = 30)$	0	0.0	
P1	5	16.7	
P2	12	40	
P3	7	23.3	
P4	4	13.3	
P5	1	3.3	
Рб	1	3.3	
P7	0	0.0	
Min. $-$ Max. (n = 30)	7.0 -	- 2.0	
Mean $\pm$ SD.	$1.22 \pm 3.57$		
Median (IQR)	3.0 (3.0 – 4.0)		

Mode of delivery $(n = 30)$	No.	%
NVD	25	83.3
CS	5	16.7

**Table (3):** Distribution of the studied cases according to mode of delivery.

**Table (4):** Descriptive of the examined patients regarding menopause (n = 30).

	Minimum–Maximum	Mean $\pm$ SD.	Median (IQR)
Menopause	1.0 - 17.0	$6.53 \pm 4.14$	6.50 (3.50 – 9.50)



**Figure (1):** Correlation between stress incontinence by Pre injection ICIQ score and age (n = 30).



**Figure (2):** Correlation between stress incontinence by Pre injection ICIQ score and Parity (n = 30).



Figure (3): Relation between stress incontinence by Pre injection ICIQ score and Mode of delivery.

BMI (kg/m2)	No.	%	
Normal (18.5 - <25)	5	16.7	
Overweight (25 - <30)	12	40.0	
Obese (>30)	13	43.3	
Min. – Max.	41.50 - 23.0		
Mean $\pm$ SD.	$4.94 \pm 30.17$		
Median (IQR)	29.0 (26.5 - 33.50)		

**Table (5):** Distribution of the examined patients regarding BMI (n = 30).

Table (6):Distribution of the studied cases according to degree of stress incontinence measured by ICIQ score<br/>(pre injection) (n = 30).

ICIQ score (Pre injection)	No.	%
Mild	3	10.0
Moderate	15	50.0
Severe	12	40.0

**Table (7):** Distribution of the studied cases according to <sup>1</sup>st and <sup>2</sup>nd injection.

ICIQ score	Post 1st injection (n = 30)		Post 2nd injection (n = 22)	
	No.	%	No.	%
Cure	8	26.7	6	27.3
Mild	3	10.0	4	18.2
Moderate	16	53.3	10	45.5
Severe	3	10.0	2	9.1

 Table (8):
 Changes in grades of stress urinary incontinence after therapy of PRP injection.

Due in it offer	2 <sup>nd</sup> injection					
Pre injection	Cure	Mild	Moderate	Severe	Improvement	Efficacy
Mild (n=3)	3	0	0	0	3	3/3(100%)
Moderate (n=15)	9	3	3	0	12	12/15(80%)
Sever (n=12)	2	1	7	2	10	10/12(83%)
Total	14	4	10	2	25	25/30(83%)

 Table (9):
 Distribution of the studied cases according to improvement after the 1st and 2nd injection (n = 30).

 Improvement
 After 1st injection
 After 2nd injection

 No
 %
 No
 %



**Figure (4):** Correlation between stress incontinence by Pre injection ICIQ score and Menopause (n = 30):







Figure (6): Distribution of the studied cases according to post injection.

Table. 8 shows that mild cases respond to treatment of PRP injection more than moderate and severe cases with efficacy of 100% of the studied cases compared to 80% in moderate cases and 83% in severe cases. The therapy efficiency is also presented in the table by disease acuity distribution pre PRP and after final PRP injection.

Table. 9 shows improvement in stress urinary incontinence after1st injection in 11 cases with percentage of 36.7 % of cases in addition to complete cure of 8 cases with percentage of 26.7 % of cases. After two injections of PRP, complete cure of 14 cases, improvement in degree of severity in 11 cases and only 5 cases not improved in grade of severity of incontinence with percentage of 16.7 % of the cases.

#### 4. Discussion

Involuntary urine loss caused by effort, physical activity, coughing, or sneezing is known as stress urinary incontinence. Females with stress incontinence might feel uneasy if they leak urine in bed. Regarding to the integral hypothesis, more essential disorder in patients of women SUI is a pubourethral ligament (PUL) disorder.

Many investigations have concluded that pubourethral ligaments might act as a growth agent vehicle that can increase the rebuilding of nexuses and sinews. It was explained that platelets display the capability to improve the development of new blood vessels that is stimulated following generation and immigration of endothelial cells from a preexisting vascular lattice and will be helpful in the handling of SUI.

So, we wanted to see how effective and feasible platelet-rich plasma injections are for treating stress urine incontinence in postmenopausal women on selected thirty (30) postmenopausal women with complaint of stress urinary incontinence.

All of thirty women had received a treatment with a Platelet Rich Plasma

injection in pubocervical fascia by specialized technique in one session and the 2nd injection was done if the patient needs after two months.

Patients' reassessment was done every two weeks after first injection by patient symptom. Patient complains and symptoms of side effects like pain, dysuria, worsening of SUI was observed.

In our study, the age of the studied subjects ranged from (47.0 - 67.0) years with mean  $(54.80 \pm \text{SD} 6.01)$  years as shown in Table 1. And there was statistically significant positive correlation between stress incontinence and age where stress incontinence severity increases in cases with old age rather than youngers as shown in figure 1.

This agrees with study done by Radzimińska et al., (2018) [8]. On 68 cases complaining of stress urinary incontinence with mean age of 53,  $2 \pm 5$ , 4 years Also, Hannestad et al., (2000) [9] concluded that incontinence prevalence peaked around middle age, with 30% of women 50-54 years old suffering from the condition. Also, the study done by Rortveit G, et al., (2003) [10] demonstrated clear modality of the growing spread of stress incontinence with increasing age

This disagrees with study done by EL-Hefnawy et al., (2011) [11] On 250 women suffering from stress incontinence to estimate variations between cases suffering from acute degrees of stress urinary incontinence against those with mild degrees and to reveal the risk factors of acuity reported that SUI did not improve or even reduce with increases in age.

In our work, the parity ranged from 2-7 in the studied subjects with mean  $(3.57 \pm SD 1.22)$  as shown in Table. 2. Our investigation showed that there was no statistically significant correlation between degree of severity of stress incontinence and parity as shown in figure 2 This agree with study done by Fritel, et al., (2005) [12] on two thousand six hundred and twenty-five women to assess the spread of acute stress urinary incontinence (SUI) between premenopausal females and to study prospective generative risk factors and concluded that The severity of SUI was similar among parous women regardless of birth number. In contrary to our study, EL-Hefnawy et al., (2011) [11] on 250 women suffering from stress incontinence documented that female with multiple childbirths have twice the risk of acute forms of the disease.

As regard to the mode of delivery of our 30 studied cases was normal vaginal delivery in 25 cases with percentage of 83.3 % of the studied cases and cesarean section delivery in 5 cases with percentage of 16.7 % of the studied cases as displayed in Table 3.

Our study showed that there were statistically significant differences in grade of severity of incontinence in relation to the mode of delivery with increasing severity in vaginal delivery more than in cases with cesarean delivery as shown in figure 3.

In agreement of study done by Rortveit G, et al., (2003) [10] that investigated 15,307 females recorded in the Epidemiology of Incontinence in the County of Nord-Trondelag (EPINCONT) investigation, this investigation reported that Vaginal delivery was related to a maximal improvement in risk. In addition, the risk of mild or acute incontinence was greater in the vaginalbirth group than in the C-section group.

In disagreement with study done by Fritel, et al., (2005) [12] on two thousand six hundred and twenty-five women to access the spread of acute stress urinary incontinence (SUI) between perimenopausal females and to study prospective generative risk factors recorded that the effect of the mode of birthhoods (spontaneous, forceps or caesarean) on grade of severity of SUI is slight and statistically insignificant.

In our study, menopausal time range from (1 - 17.0) years with mean  $(6.53 \pm \text{SD} 4.14)$  years as seen in Table 4, and there was statistically significant positive correlation between stress incontinence and

menopause where stress incontinence severity increases in cases with long menopausal time as shown in figure 4.

These agree with study by Long et al., (2021) [13] while mean menopausal time was 5 years. In contrary to our study done by EL-Hefnawy et al., (2011) [11] and demonstrated the menopausal status did not represent any additional risk of increasing stress incontinence severity.

The mean BMI of our 30 studied cases was  $30.17 \pm 4.94$  kg/m<sup>2</sup> with minimum BMI 23.0 kg/m2 and maximum was 41.50 kg/m2 as shown in Table 5. Our study shows that there was no statistically significant correlation between stress incontinence and BMI as shown in figure 5. In agreement with work the study done by Lau et al., (2019) [14] which is a retrospective study examined the objective and subjective treatment rates of obese and overweight women who underwent sling operations and had a mean BMI  $29.5 \pm 6.17$ kg/m2

In disagreement of our work, the study done by Richter, et al., (2005) [15] That aimed to identify factors associated with urinary incontinence severity at baseline in women undergoing surgery for stress incontinence documented that the severity of urinary incontinence was positively associated with higher BMI.

Our thirty postmenopausal women classified according to degree of severity of stress incontinence measured by ICIQ score. 3 cases were mild with percentage of 10 % of cases, 15 cases were moderate with percentage of 50 % of cases and 12 were severe with percentage of 40 % of cases as shown in Table 6.

In the current study we found that PRP is effective treatment for SUI with success rate of the treatment 83 % and most cases experienced a lower degree of SUI immediately following the first PRP injection as shown in Table. 8.

Nikolopoulos, et al., (2016) [16] agree with our study in their medical hypothesis concluded that as pubourethral ligament disorders lead to stress incontinence, recuperation of the anatomy of this nexus could have a therapeutic influence on this condition. The assistance of growth agents appears to be critical through this procedure and PRP is a facilely prepared, comparatively low coat solution.

These go with a study done by Neto. et al., (2017) [17] a pilot trial records the echo of females with stress incontinence. overactive bladder, lubrication and erotic dysfunction (libido, arousal, dyspareunia) to estimate the safety, tolerability and clinical efficiency of "O-Shot" Platelets Rich Plasma (PRP) of the vaginal area of the vul. PRP has newly been displayed to increase regenerate senility of skin using many growth agents and cell molecular cohesions involving thirteen patients complaining of stress urinary incontinence recorded more than 90% relief of the symptoms after treatment with PRP. Cases received two injections two months apart also.

Our study documented improvement in stress urinary incontinence after1st injection in 11 cases with percentage of 36.7 % of cases in addition to complete cure of 8 cases with percentage of 26.7 % of cases. After the second injection of PRP, cure of 14 cases complete with improvement in degree of severity in 11 cases. And only 5 cases not improved in grade of severity of incontinence with percentage of 16.7 % of the cases as shown in Table .9.

In agreement to our work, a study done by Long, et al., (2021) [13] that aimed to estimate the efficacy of regional injection of autologous platelet rich plasma (A-PRP) as a handling for females suffering from stress urinary incontinence (SUI). In this potential intervention trial, 20 consecutive females suffering from SUI were cured with A-PRP injection at the frontal vaginal wall where mid-urethra is located; their average age was 44.5 years old, with 1.6 times average parity and a BMI of 22.7 mg/m2. Five or 25% of them are menopause. The study demonstrates A-PRP is effective in treating women with SUI. But in contrary the study had done for as long as 6 months post treatment.

#### 5. Conclusion

The present study revealed that Local injection of autologous platelet rich plasma has a curative effect on females suffering from stress urinary incontinence with high efficacy and success rate.

#### References

- Rakowska-Silska M, Jobs K, Paturej A, et al. (2020): Voiding Disorders in Pediatrician's Practice. Clin Med Insights Pediatr. 14:1179556520975035.
- Dumoulin C, Adewuyi T, Booth J, et al. (2017): Adult Conservative Management. In: Abams P, Cardozo L, Wagg A, et al (eds). Incontinence. 6<sup>th</sup> ed. Bristol UK: International Continence Society. p. 1445-628.
- Russo E, Caretto M, Giannini A, et al. (2021): Management of urinary incontinence in postmenopausal women: An EMAS clinical guide. Maturitas. 143:223-30.
- 4. Amable PR, Carias RB, Teixeira MV, et al. (2013): Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem cell Res Ther. 4(3):67.
- 5. Wang SZ, Chang Q, Lu J, et al. (2015): Growth factors and plateletrich plasma: promising biological strategies for early intervertebral disc degeneration. Int Orthop. 39:927-34.

- Fang J, Wang X, Jiang W, et al. (2020): Platelet-Rich Plasma Therapy in the Treatment of Diseases Associated with Orthopedic Injuries. Tissue Eng Part B Rev. 26(6):571-85.
- 7. Martínez CE, Smith PC, Palma Alvarado VA. (2015): The influence of platelet-derived products on angiogenesis and tissue repair: a concise update. Front Physiol. 6:290.
- 8. Radzimińska A, Strączyńska A, Weber-Rajek M, et al. (2018): The impact of pelvic floor muscle training on the quality of life of women with urinary incontinence: a systematic literature review. Clin Interv Aging. 13:957-65.
- Hannestad YS, Rortveit G, Sandvik H, et al. (2000): A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trondelag. J Clin Epidemiol. 53: 1150.
- Rortveit G, Daltveit AK, Hannestad YS, (2003): Hunskaar S. Urinary incontinence after vaginal delivery or cesarean section. N Engl J Med. 348:900–7.
- EL-Hefnawy AS, Wadie BS. (2011): Severe stress urinary incontinence: Objective analysis of risk factors.Maturitas. 68(4): 374-7.
- Fritel X, Ringa V, Varnoux N, et al. (2005): Mode of delivery and severe stress incontinence. A cross-sectional study among 2625 perimenopausal women. BJOG: An Int J Obstet Gynaecol. 112: 1646-51.

- Long CY, Lin KL, Shen CR, et al. (2021): A pilot study: effectiveness of local injection of autologous platelet-rich plasma in treating women with stress urinary incontinence. Sci Rep. 11: 1584.
- Lau HH, Enkhtaivan S, Su TH, et al. (2019): The Outcome of a Single-Incision Sling versus Trans-Obturator Sling in Overweight and Obese Women with Stress Urinary Incontinence at 3-Year Follow-Up. J Clin Med. 8(8):1099.
- 15. Richter HE, Litman HJ, Lukacz ES, et al. (2011): Demographic and clinical predictors of treatment failure one year after midurethral sling surgery. Obstet Gynecol. 117:913–21.
- 16. Nikolopoulos KI, Pergialiotis V, Perrea D, et al. (2016): Restoration of the pubourethral ligament with platelet rich plasma for the treatment of stress urinary incontinence. Med Hypotheses. 90:29-31.
- Neto JB. (2017). O-Shot: Platelets Rich Plasma in Intimate Female Treatment. J Women's Health Care. 6:5.