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The Role of Platelet Rich Plasma Injections in Cases of Stress Incontinence

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Abstract

Stress urinary incontinence is extremely bothersome and can lead to significant interference in the quality of life in the women. This study aims to suggest the role of platelet-rich plasma as a novel potential minimally invasive treatment for women suffering from stress urinary incontinence (SUI). In a prospective interventional study was conducted at Sayed Galal hospital on 20 patients seeking treatment for urinary stress incontinence were treated with autologous Platelet Rich Plasma injection at anterior vaginal wall, close to external urethral sphincter. Self-reported questionnaires were used to measure pre-treatment, 1 month and 3 months post-treatment symptom severity. The results are analyzed with valid statistical methods. Bivariate analysis revealed a significant incontinence improvement at both 1 month and 3 months post treatment without significant adverse reactions reported. No significant changes before and after the treatment were reported by the patients regarding sexual function by Female Sexual Function Index (FSFI) questionnaire. The result suggested that Local injection of autologous platelet rich plasma is a considerable treatment option in treating women with Stress urinary incontinence. It also opens up further research opportunities for autologous platelet rich plasma in clinical applications.

Introduction: Urinary incontinence can impact women's social, physical, mental and sexual wellbeing, and lead to depression and social isolation. Stress urinary incontinence (SUI) refers to the involuntary leakage of urine accompanying physical exertion (i.e. coughing, exercise, and sneezing). It is commonly acquired after pregnancy and childbirth due to weakening of the pelvic floor muscles that support the urethra against the anterior vaginal wall. Current SUI treatment includes surgery to re-establish sufficient urethral resistance in order to prevent urine leakage during increased intra-abdominal pressure. The mid-urethral sling (MUS) has become the preferred procedure, as it is less invasive than the Burch colposuspension. However, the MUS procedure has a 5–20% failure rate and carries risks such as infection, voiding dysfunction, hemorrhage, pain, bladder or urethral injury, and mesh erosion.

Hence, there is a need for alternative efficacious, outpatient SUI treatments.

Platelet-derived therapies are a growing trend across multiple medical and surgical specialties. Evidence suggests that platelets play an important role in tissue repair, vascular remodeling and immune responses through secretion of growth factors, cytokines and chemokines. These biologically active proteins include transforming growth factor-β, platelet-derived growth factor, platelet-derived epithelial growth factor, insulin-like growth factor, vascular endothelial growth factor. These

growth factors are implicated in many aspects of natural wound healing, including chemotaxis, cell proliferation, and cell differentiation. The key role of platelets in these processes makes them an attractive candidate for therapies aimed at accelerating natural healing. One of the most well described platelet-based therapies is autologous platelet-rich plasma (PRP). PRP is derived from the centrifugation of whole blood with a separator gel to remove the red and white blood cells. The resulting supernatant has a greater than four-fold increase in platelets and other plasma proteins. This concentrate is then administered via injection. An immediate response to the PRP injections in the anterior vaginal mucosa is the increase in the blood flow, vascular permeability, and interstitial edema, which will result in periurethral tissue tumescence for approximately 48 hours. These changes are followed by fibroblastic and myofibroblast activation. The stimulus on the fibroblasts triggers the formation of new collagen fibers and the tightening of the anterior vaginal wall. The preparation of PRP depends on the type of device chosen and should be done according to the manufacturer's instructions (Table 1).

Devices	Blood collection/ anticoagulant	Centrifugation	
		number of times	speed/time
Selphyl®	Tube 9 mL/sodium citrate	1	1,100 g/6 min
PRGF Endoret®	Tube 9 mL/sodium citrate	1	270 g/7 min
Cascade®	Tube 9 mL/sodium citrate	2	1,100 g/6 min 1,450 g/15 min
Golden VAC	Tube 8.5 mL/sodium citrate + gel	1	1500g/5 min, 3000g/10 min
Plateltex®	Tube 9 mL/ACD	2	180 g/10 min 1,000 g/10 min
Regenkit®	Tube 9 mL/sodium citrate	1	1,500 g/9 min
ACP Arthrex®	Syringe 15 mL/ACD or no anticoagulant	1	1,500 rpm/5 min
GPS III®	Syringe 30 or 60 mL/ACD	1	3,200 rpm/15 min
Genesis®	Syringe 12 mL/ACD	1	2,400 rpm/12 min
SmartPrep 2®	Syringe 20 or 60 mL/ACD	2	2,500 rpm/4 min 2,300 rpm/10 min
Proteal®	Syringe 20 mL/sodium citrate	1	1,800 rpm/8 min
Magellan®	Syringe 30–60 mL/ACD	-	-
Angel®	Syringe 40–180 mL/ACD	-	-
ACD, acid citrate dextrose. adapted from Dohan Ehrenfest, 2013			

Table 1 - The different PRP systems that facilitate the preparation of PRP .

As described in Table 1, there are different PRP systems that facilitate the preparation of PRP in a reproducible manner. All operate on a small volume of drawn blood and on the principle of centrifugation. Briefly, the procedure requires the use of relatively small volumes of blood. The PRP is obtained from the blood of patients before centrifugation. The whole blood is obtained by venipuncture in anticoagulated tubes (usually with acid citrate dextrose or sodium citrate solution). The blood is then centrifuged with single or a double spin centrifugation, depending on the device. The settings of the centrifuge established to obtain PRP at an adjustable concentration are defined by the manufacturer and cannot be changed by the physician. After centrifugation, the tube shows 3 basic layers: at the bottom of the tube, there are red blood cells with leukocytes deposited immediately above; the middle layer corresponds to the PRP, and at the top, there is the PPP, The poor platelet plasma is removed, and platelet rich plasma is obtained. Platelets can be activated before

application of the PRP, although there is no consensus on whether or not platelets must be previously activated before their application and with which agonist. Thrombin and calcium chloride, which are aggregation inducers, are used with the aim to activate platelets and stimulate degranulation, causing the release of the GFs, Some authors activate platelets, whereas others apply platelets without previously activating them, arguing that better results are obtained. Recent studies found that the use of such aggregators is not necessary because at the time of administration, the platelets are automatically released and ready to exert their function. Even though most devices aim to obtain the best PRP, the systems differ extensively in their ability to collect and concentrate platelets depending on the method and time of its centrifugation. As a result, suspensions of different concentrations of platelets and leucocytes are obtained. It is difficult to assess which kit for PRP preparation is better and which is worse**.** In addition, each preparation may produce different types of PRP with different applications, there is no consensus about the number of centrifugations required, nor on their speed duration. There is intensive ongoing debate regarding the ideal volume of PRP to administer, the frequency of application, the exact site of administration of PRP, and which technique/preparation system of manufacture to use.

Aim of the Work: To suggest the role of platelet-rich plasma as a novel potential minimally invasive treatment for SUI

Study design: This prospective interventional study was conducted at Sayed Galal hospital for one year (February 2021-January 2022) on 20 patients seeking treatment for urinary stress incontinence who attended the clinic or were admitted to the hospital. Patients were chosen to be included in the study according to the following criteria any female patient with mild to moderate SUI above 35 years old, with exclusion of those who were under anti-platelet agent treatment, platelet dysfunction syndrome, critical thrombocytopenia, acute and chronic infections, collagen disease, anti-coagulation therapy and history of malignancy.

All patients work up: Detailed history: Personal history, Present history, Obstetric history, medical history, surgical history, allergic history and drug usage. Complete physical examination: general assessment, abdominal examination and local examination. Investigation such as CBC, urine analysis, urine C&S, LFT, KFT, pelvic abdominal ultrasound and urodynamics (before and after PRP injection). Before enrollment, the patients marked informed consent for participation. The primary outcome was the degree of SUI relief objective assessment of urinary incontinence severity by visual analog scale, while the secondary outcome assesses net change of daily pad use, net change of the subsequent parameters from baseline to three months after the treatment day: maximum flow rate; residual urine; first sensation to void; maximum cystometric capacity and detrusor pressure at peak flow. Urodynamics study were planned for them before and three months after treatment. Questionnaires that evaluate the severity of their urinary incontinence and sexual dysfunction were International Consultation on Incontinence Questionnaire-Short Form, Urogenital Distress Inventory, Incontinence Impact Questionnaire, Overactive Bladder Symptom Scores and Female Sexual Function Index. In particular, ICIQ-SF was the primary tool for assessing SUI severity, which was categorized into slight, moderate, and severe according to the total points obtained after answering the questionnaire. The cut-of values were 1–5, 6–12, and, 13–18 points for mild, moderate, and severe, respectively.

Equipment's used: 5 cc syringes, Centrifuge, 30 G ½ needles, betadine vaginal douche, Golden VAC PRP tube with separator gel, and numbing cream (topic anesthesia).

Technique: The study utilized marketed PRP kit (golden VAC). PRP was prepared according to the standardized methodology instructed by the kit. The tube was utilized to gather individual patient's entire blood, 15 cc blood sample was

suctioned from the patient's peripheral vein in vacuum assortment tube with separator gel, which is centrifuged separating red and white cells at 3000 RPM for 10 minutes. Platelet cells were on top of the tube and the 4 cc of cells suspension are called Platelet Rich Plasma. The patients were set in a dorsal lithotomy position then disinfection was applied with betadine at the sites of injections. roughly 5 minutes before the procedure a topical anesthetic was applied in the anterior vaginal wall covering the urethral meatus, paraurethral, suburethral, and lateral urethrovaginal areas. After isolation of the PRP injection of 8 mm by a 5 cc syringe with 30 G needle into anterior vaginal wall, close to external urethral sphincter three points on each side. Injection in paraurethral area with depth 10 mm from lateral to external urethras orifice.
While performing the maneuvers and 24 hours after the ending, patients were assessed for pain using the visual analog scale and numerical rating scale for evaluating pain intensity. There were no unfavorable impacts or complications related to the techniques. The evaluation of pain was negative, none of the patients complained of pain during the techniques or up to 24 hours after it. Clinical assessment after treatment revealed no functional alterations or hypertrophic scarring. The average procedure time was 15 minutes and no prophylaxis antibiotics were utilized.

Data Analysis: Information were gathered, recorded, coded, coordinated and afterward entered to a Microsoft Excel sheet then analyzed to give last study results using the IBM Corp. Released 2013. IBM Statistical Package for Social Sciences (SPSS) Statistics, Version 28th (2021). Normally distributed continuous data was expressed as mean + standard deviation. Categorical data was shown as frequency and percentage. Data were introduced as tables and diagram. Statistical analysis was performed utilizing Student's t-test and paired t-test. Results were considered statistically significant at a p-value of less than 0.05.

Ethical Considerations: Approval of faculty's ethical committee: This study was only carried out after getting approval of the ethical committee in Faculty of Medicine, Al Azhar University as the study aims, strategy and measurements were politically accepted and furthermore to work with any issue. Socially satisfactory methodology and measurements. Confidentiality of the gathered data: Just for research use, no different tests or DNA analysis were done by serum samples, Serum samples were disposed at the end of research. Good communication channel among researchers and target population by: Giving background regarding the aim of study, Stress on confidentiality of information. Acceptance of all the participants was acquired by written informed consent in a simple justifiable language.

Result: Among the 20 patients enrolled, the average age was 48.65 years old with averaged parity of 4.65 times, body mass index 29.4 mg/m2. 50% of patients are menopause. Prior to the PRP treatment, the average pad test was 5.35 g; two (10%) reported mild symptom while 15 (75%) and 3 (15%) reported moderate and severe diseases, respectively by International Consultation on Incontinence Questionnaire-Short Form score. All patients followed for at least 3 months (Table 2).

Mean age (Years)	48.65 ± 6.9
Mean parity	4.65 ± 5.5
Mean BMI (kg/m)	29.4 ± 10.9
Pad test	5.35 ± 1.2
Menopause	10 (50%)
SUI grade (ICIQ-SF)	
Mild	2
Moderate	15
Severe	3
Follow up (months)	3

Table 2 - Demographic data

Values are expressed as mean ± standard deviation or numbers.

SUI grade according to ICIQ-SF: slight (1–5), moderate (6–12), severe (13–18).

Treatment efficacy assessed by International Consultation on Incontinence Questionnaire-Short Form , Urogenital Distress Inventory , Incontinence Impact Questionnaire and Overactive Bladder Symptom Scores showed significant incontinence improvement at both 1 month and 3 months post treatment (Table 3).

N = 20	**Baseline**	**1 months post-Tx**	**3 months post-Tx**	**P value***	
				1 month	**3 month**
ICIQ-SF	12 ± 2.9	7 ± 1.8	5 ± 1.4	0.012*	0.002*
UDI-6	35 ± 6.9	24 ± 5.3	16 ± 4.6	0.005*	0.004*
IIQ-7	24 ± 5.3	12 ± 2.9	10 ± 1.3	0.001*	0.016*
OABSS	6 ± 1.2	3 ± 0.5	4 ± 0.5	0.034*	0.044*

Table 3 - Questionnaire results at baseline and 1, 3 months post-treatment.

Tx treatment, ICIQ-SF International Consultation on Incontinence Questionnaire-Short Form, UDI-6 Urogenital Distress Inventory, IIQ-7 Incontinence Impact Questionnaire, OABSS Overactive Bladder Symptom Scores.

Values are expressed as mean ± standard deviation

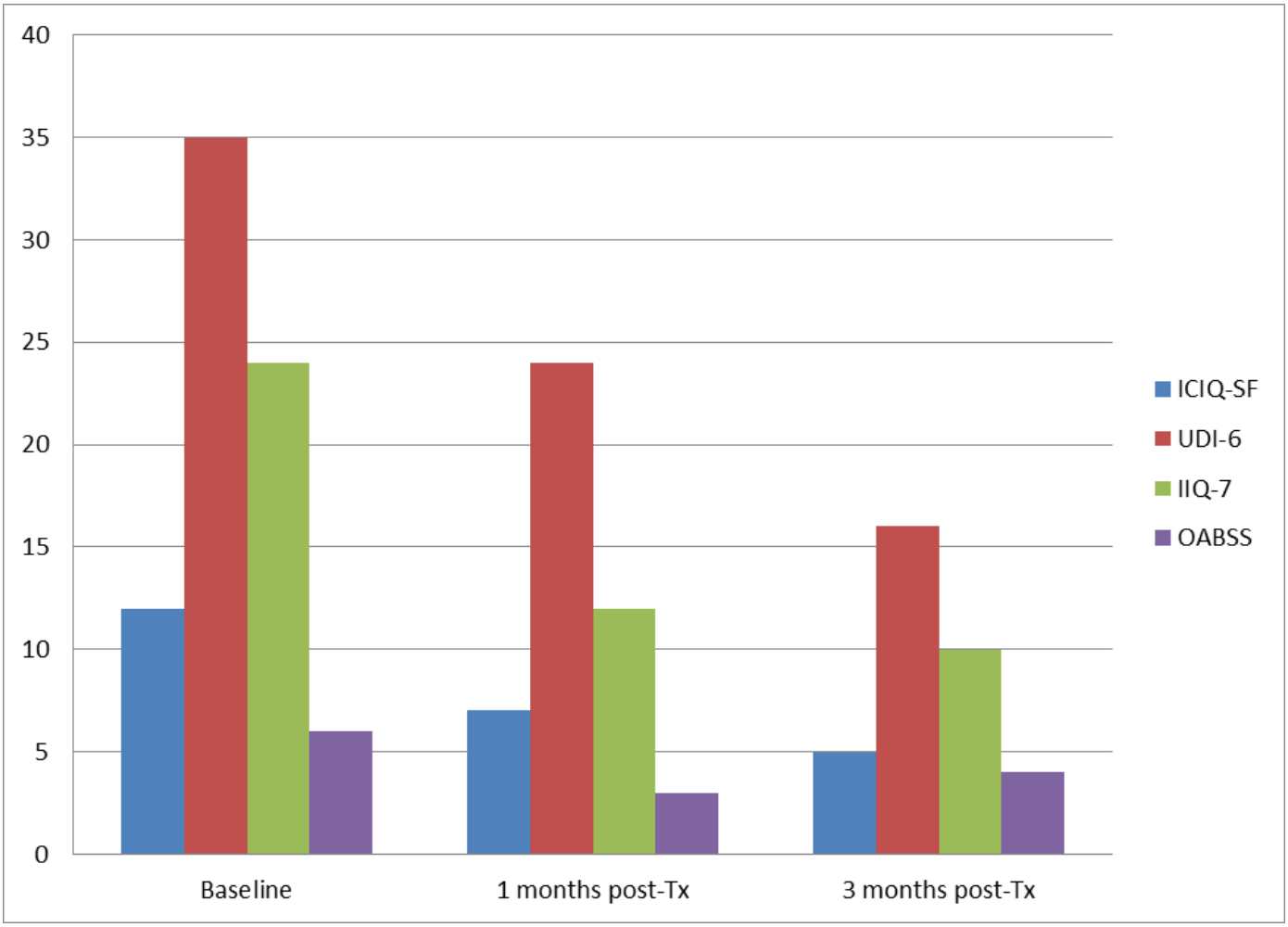

Figure 1 - Questionnaire results at baseline and 1, 3 months post-treatment showed significant incontinence improvement at both 1 month and 3 months post treatment.

Changes in grades of SUI following treatment of PRP injection were shown in Fig. 2.

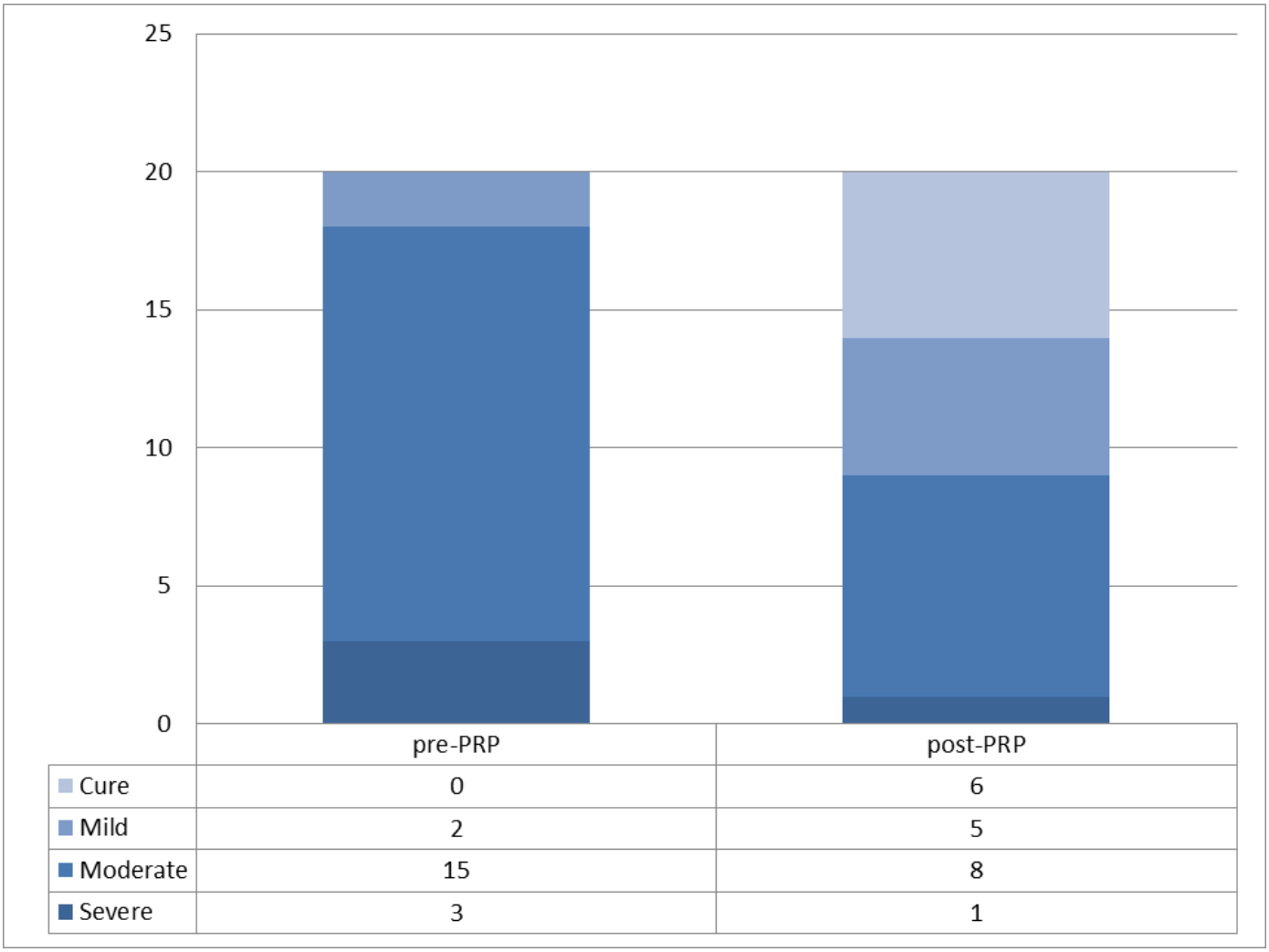

Figure 2 - Changes in grades of stress urinary incontinence following treatment of PRP injection.

These women were then sorted by age, with the cut-of value at 50 years old to investigate age as a factor for treatment efficacy. (Table 4).

The result showed no significance between the characteristics of the two groups in terms of mean body mass index, underlying diabetes mellitus, parity number and history of hysterectomy.

	Age < 50	Age ≥ 50
Mild	1	1
Moderate	8	7
Severe	1	2
Improved	7	6
Unchanged/Worse	3	4
Efficacy	70%	60%

Table 4 - Changes in grades of stress urinary incontinence following treatment of PRP injection with patients' age.

However, it seems to have a trend that treatment success rate with cured and improved symptoms was slightly higher in the younger group (70%) compared to that of the older group (60%), although it did not reach statistical significance (P=0.07).

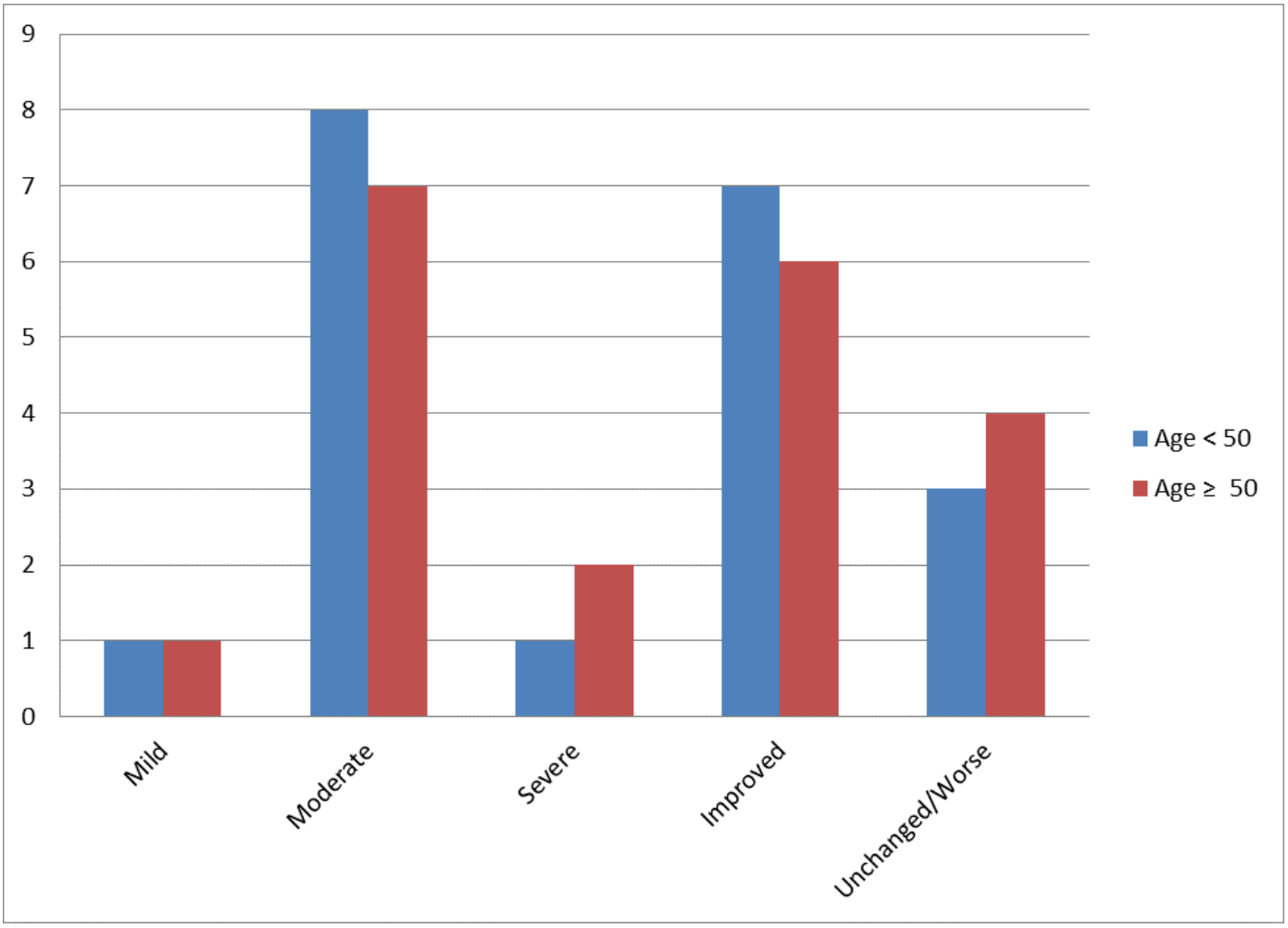

Figure 3 - Changes in grades of stress urinary incontinence following treatment of PRP injection with patients' age.

The treatment efficacy is also demonstrated by disease severity distribution pre-PRP and 3 months post-PRP (Table 5), with a shift of the majority reporting moderate and severe diseases to moderate and milder diseases.

Pre-op	Post-op						
	Cure	Mild	Moderate	Severe	Improved	Unchanged/Worse	Efficacy
Mild (n=2)	2	0	0	0	2	0	100%
Moderate (n=15)	4	5	6	0	9	6	60%
Severe (n=3)	0	0	2	1	2	1	66.6%
All (n=20)	6	5	8	1	13	7	65%

Table 5 - Treatment efficacy of PRP injection.

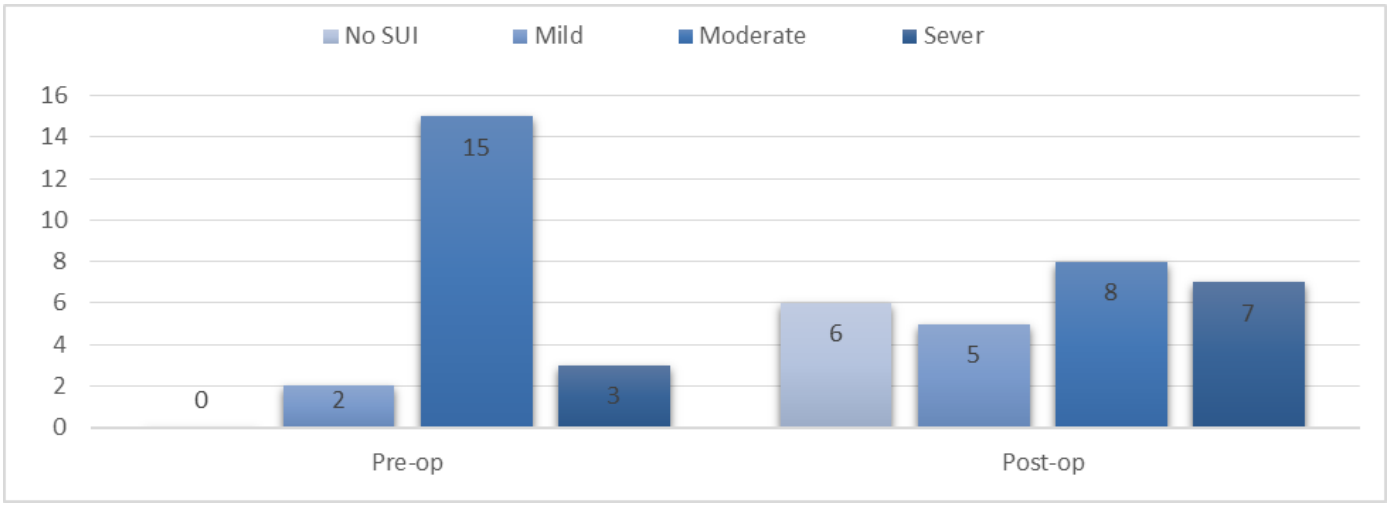

Figure 4 - Treatment efficacy of PRP injection.

Only 10 women completed the urodynamics studies before and 3 months after intervention. Residual urine and bladder volume at first sensation to void increased significantly after injection of PRP (Table 6).

Parameters	Pre-op (n = 10)	Post-op (n = 10)	P value #
Qmax (ml/s)	28.8 ± 4.6	31.4 ± 4.6	0.08
RU (ml)	9.7 ± 5.1	46.7 ± 13.4	0.028 §
FS (ml)	135.8 ± 42.5	163.8 ± 17.0	0.001 §
MCC(ml)	437.0 + 26.2	412.6 ± 51.8	0.17
Pdet (cmH2O)	26.2 ± 6.4	24.8 ± 6.8	0.52
FUL (mm)	23.9 ± 6.1	24.7 ± 6.6	0.22
MUCP (cmH2O)	55.5 ± 9.2	44.1 ± 19.5	0.14

Table 6- Urodynamics changes before and 3 months after PRP treatment.

Data are given as mean ± standard deviation.

PRP, platelet-rich plasma; DO, detrusor over activity; Qmax, maximum flow rate; RU, residual urine; FS, first sensation to void; MCC, maximum cystometric capacity; Pdet, detrusor pressure at peak flow; FUL, functional urethral length; MUCP, maximum urethral closure pressure.

#Paired t-test; § significant significance.

All other urodynamics parameters showed no significant differences following treatment (Fig 5).

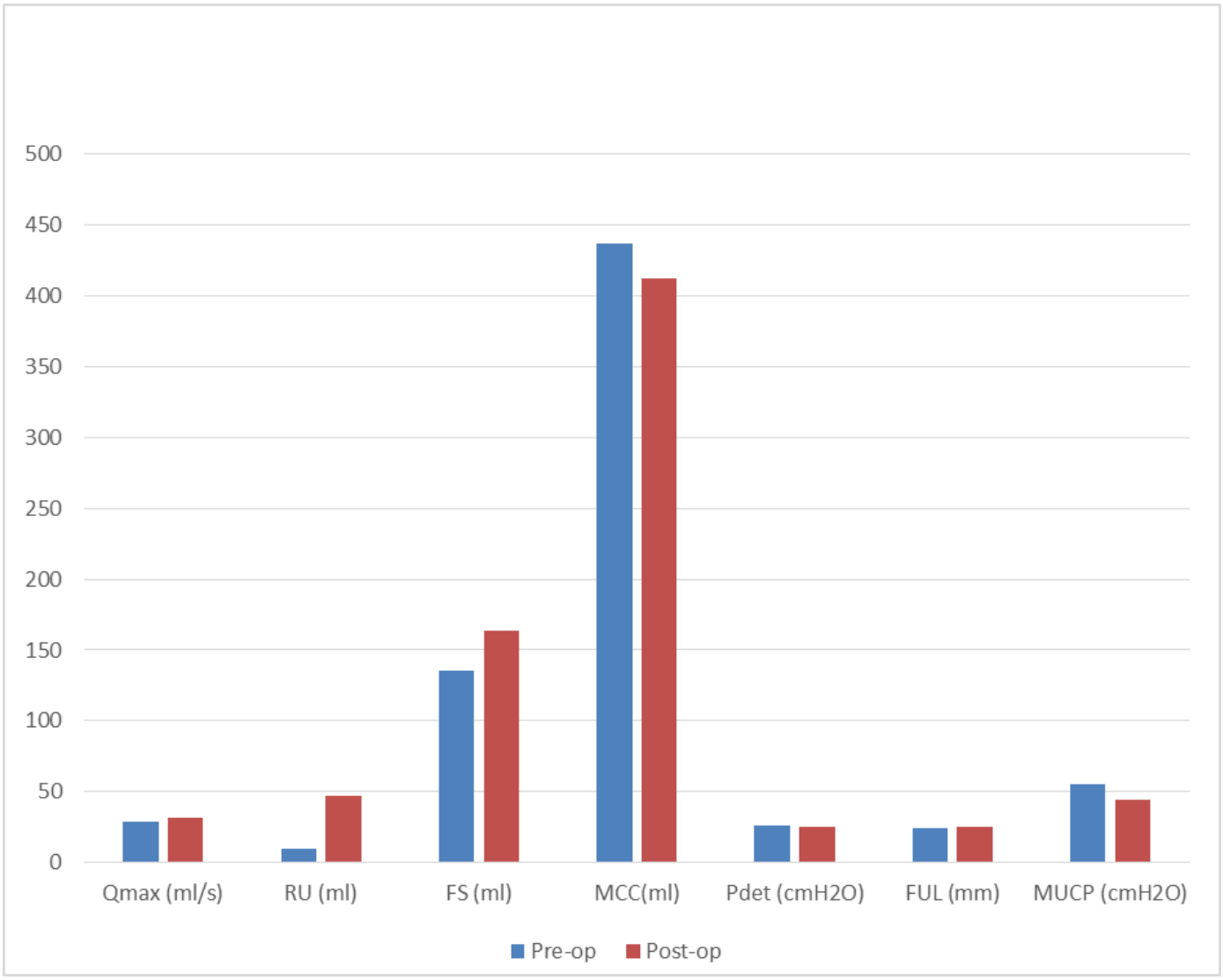

Figure 5 - Urodynamics changes before and 3 months after PRP treatment.

The influence of PRP injection on sexual function was investigated by Female Sexual Function Index (FSFI) questionnaire.

No significant changes before and after the treatment were reported by the patients. (Table 7).

	Pre-treatment	3 months post-treatment	P value
Desire	2.7±1.3	3.9±2.4	0.79
Arousal	2.6±1.8	2.9±0.9	0.46
Lubrication	3.2±2.1	3.5±2.1	0.34
Orgasm	3.0±1.9	3.4±2.1	0.35
Satisfaction	3.2±2.0	3.8±2.3	0.13
Pain	3.2±2.0	3.9±2.4	0.11
FSFI total scores	17.9±10.2	20.3±11.0	0.25

Table 7 - Changes Female Sexual Function Index (FSFI) scores at baseline and 3 months post-treatment with PRP injection.

No significant changes before and after the treatment were reported by the patients. (Figure 6).

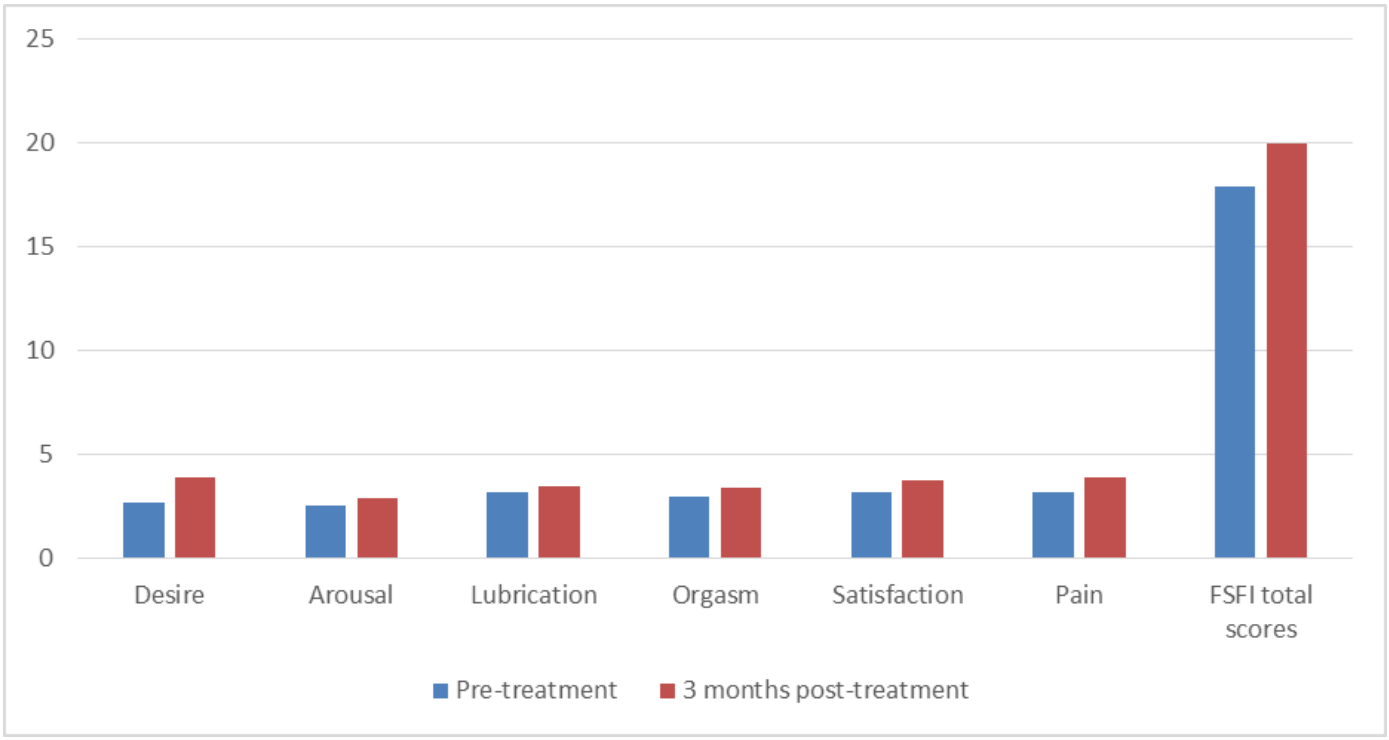

Figure 6 - Changes Female Sexual Function Index (FSFI) scores at baseline and 3 months post-treatment with PRP injection.

Discussion: The current study shows that the PRP is effective in treating women with SUI for as long as three months post treatment. Among the 20 patients enrolled, the average age was 48.65 years old with averaged parity of 4.65 times, body mass index 29.4 mg/m2. Preceding to the PRP treatment, the average pad test was 5.35 g. Two patient (10%) reported mild symptom while 15 patient (75%) and 3 patient (15%) reported moderate and severe diseases, respectively by International Consultation on Incontinence Questionnaire-Short Form score. After the PRP treatment, the average pad test was 2.55 g; 6 patient (30%) cured, 5 patient (25%) reported mild symptom while 8 (40%) reported moderate and only one patient (5%) severe diseases, by (ICIQ-SF) score. Treatment efficacy evaluated by ICIQ-SF, UDI, IIQ and OABSS showed significant incontinence improvement at both one month and three months post treatment, the mean value of ICIQ-SF before treatment was 12 and 3 months post treatment was 5, with significant change (p value 0.002), Improvement occurred in 13 patients with no change in 7 patients. A secondary analysis of this study observed a superior treatment outcome in the patient group younger than 50 years old. However, it seems to have a trend that treatment success rate with cured and improved symptoms was slightly higher in the younger group (70%) compared to that of the older group (60%), although it did not reach statistical significance (P=0.07). It is postulated that being younger might pose better rejuvenating abilities, and thus better treatment effect of A-PRP. Also, aged patients are likely to be impacted with additional variables such as menopausal state, more severe SUI symptoms and more underlying systemic conditions such

as diabetes mellitus and hypertension, history of hysterectomy, abdominal surgeries and previous anti-continence treatments. These potential confounding factors are demonstrated by a trend in our small study groups, although not reaching statistical significance. Further study with greater patient number and variable-adjusted analysis is required to validate the assertion. If proven, these factors would be very helpful for patient selection that will benefit the most from PRP treatment. Sexual function is intimately related to urinary incontinence, thus warranting a secondary analysis in the treatment of SUI with A-PRP. The current study utilizes FSFI questionnaires pre- and post-PRP treatment but failed to reveal significantly improved composite sexual function score, regardless the length of follow up. The mean value of FSFI before treatment was 17.9 and 3 months post-treatment was 20.3; with a non-significant change (p value 0.25).

Stress urinary incontinence impacts the patient's self-image, confidence and fear of embarrassment when it comes to sexual functions. Therefore, an improvement in SUI symptoms readily enhances sexual desire. Interestingly, our finding is in contrary to that.

The results of this study are in agreement with those of **(João Brito Jaenisch Neto, et al)** which measure the response of women with stress incontinence, overactive bladder, lubrication and sexual dysfunction (libido, arousal, dyspareunia) to evaluate the safety, tolerability and clinical efficacy of "O-Shot" Platelets Rich Plasma (PRP) of the vulvo vaginal field. The results of this study show that about sixty-eight women in the age ranging from 32 to 97 (average: 62.8 years old) were enrolled in this study. Of the sixty-eight patients, 94% of them were satisfied, only 6% of them with overactive bladder did not have any improvement with this treatment. And this study demonstrates that Platelet Rich Plasma, "O-Shot" is an office treatment that is safe, effective, non-surgical, and non-hormonal option for women having stress incontinence, overactive bladder, lack of lubrication, and sexual dysfunction, such as lack of libido, arousal or dyspareunia.

Similar to this study, **Ariel Luksenburg, Juan J. Barcia, Roberto Sergio, et al** studied "Stress Urinary Incontinence: Treatment with Platelet-Rich-Plasma Injection and Placement of Polydioxanone Threads". A total of 23 patients with mild urinary incontinence, mean age 46, were evaluated with detailed history, examination, urinary diary, complete laboratory tests, ultrasonography, urodynamics studies, and completion of International Consultation on Incontinence Questionnaire Short Form. Under local anesthesia, PRP was injected through the anterior vaginal wall, PDO threads placed in paraurethral, suburethral, and lateral urethrovaginal spaces, using instruments developed for safe and effective performance. Patients were analyzed at 1, 2, 4, 8 weeks and 6 months posttreatment. A total of 10 patients were biopsied preoperatively and 60 days after treatment. Symptoms and ICIQ-UI SF score were significantly improved. Postoperative urodynamics studies were normal in all cases. Biopsies after treatment showed a dense connective tissue tridimensional mesh. The minimally invasive technique presented here results in strengthening of the paraurethral, suburethral, and lateral urethrovaginal spaces and the mucosa of the anterior vaginal wall. The combination of PRP injections and the placement of PDO threads creates a fibrotic and absorbable mesh-like structure, aimed to increase the urethral resistance, so that under effort the intravesical pressure does not overcome the urethral pressure.

Unlike the current study, **Charles Runels, Hugh Melnick, et al.** examined the Effect of Localized Injections of Autologous Platelet Rich Plasma (PRP) for the Treatment of Female Sexual Dysfunction.

Its report demonstrate significantly improved FSFI performance in total scores, desire, arousal, lubrication and orgasm in women receiving PRP injection for sexual disorders. The authors also reported prolonged arousal, ejaculatory orgasm, and spontaneous orgasm in younger women as side effects that resolve in 2 weeks without treatment. The observation is

not revealed by our study that aimed at treating urinary incontinence, which is mainly attributed to disparity in injection sites. Runels' group, who specifically aimed at treating sexual dysfunctions, injected A-PRP at both clitoris and a spot of anterior vaginal wall.

Due to the paucity of data and research on this new issue, there were few articles addressing the impact of PRP on female Urinary incontinence. Limitations of the work included small sample size and lack of a controlled group. Future work is encouraged to incorporate a randomized controlled trial with longer follow-up period.

Comparative study with head-to-head comparisons to other bulking agents is plausible. Other potential areas to investigate may include A-PRP as a preventative role at the time of pelvic floor structure insult, as an adjuvant modality in combination with corrective surgery or other conservative treatments, determination of its lowest effective dose, repeat treatment intervals if necessary and long-term efficacy.

Conclusion: Local injection of autologous platelet rich plasma is an effective, affordable, minimally invasive procedure, safe with somewhat satisfactory response in treating women with SUI. Follow up for those patients to detect the time validity of the treatment and if re-injection is recommended. Until now, how long the treatment effect could sustain remains unknown!

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