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ORIGINAL ARTICLE

Intracavernosal Platelet Rich Plasma with Phosphodiesterase Type 5 Inhibitors Versus Phosphodiesterase Type 5 Inhibitors in Management of Erectile Dysfunction: A comparative randomized study.

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ABSTRACT

Keywords: Erectile dysfunction , platelet rich plasma , Phosphodiesterase type 5 inhibitors.

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Background: Erectile Dysfunction (ED) is defined as inability to achieve and/or maintain an erection sufficient for satisfactory sexual performance.**Objective:**To assess the use of intracavernosal injection of platelet rich plasma (PRP) with and without oral Phosphodiesterase type 5 inhibitors for treatment of ED.**Methods:**A prospective randomized study included 38Patients. They were randomly allocated in two groups, 19 each.The two group was treated by daily Phosphodiesterase type 5 inhibitors (tadalafil 5 mg). Group A had intracavernosal injection of PRP, while group B had saline 0.9% (placebo). All patients answered the Arabic version of IIEF-5 questionnaire in structured interview before and 3 months after initiation of therapy.**Results:**Themean ILEF-5 score in group A was 9.84 before which increased to 17.6 after injection (p-value<0.001), Meanwhile the mean ILEF-5 score in group B before injection was 9.89 and after injection was 12.9 (p-value <0.001). Furthermore, the mean difference for (ILEF-5) score between both groups after injection was 4.68 (p-value < 0.014).**Conclusion:** ICI of PRP with PDE5 inhibitors improve erectile function and patient satisfaction more than PDE5 inhibitors alone and might be an optional treatment for patients with erectile dysfunction.

INTRODUCTION

Erectile Dysfunction (ED) is defined as inability to achieve and/or maintain an erection sufficient for satisfactory sexual performance,(1)The prevalence of ED is 20-30 % among men aged between 40-80 years (2), while it is >40% among Arab men. (3). The prevalence of ED increases with age and other risk factors (hypertension, diabetes, smoking, coronary heart disease, obesity dyslipidemia and depression)(4). Erectile dysfunction is classified as organic (i.e., neurogenic, endocrinological, vasculogenic, or drug induced), psychogenic or mixed psychogenic and organic. ED is usually of a mixed psychogenic and organic nature(5).Vascular insufficiency is probably the most common cause of organic male sexual

dysfunction (6). Phosphodiesterase type 5 inhibitors (PDE5Is) are the drug of choice for medical management of ED(7). PDE5Is work by blocking the breakdown of cyclic guanosine monophosphate, which leads to vascular tone modulation and vasorelaxation in the vascular smooth muscle of the penis. These drugs require the presence of sexual arousal and nitric oxide production. Their effect also requires the presence of adequate and efficient smooth muscle cells in the corpora cavernosa.(8).Damage to the endothelial lining of the arterial walls impairs the nitric oxide (NO) pathway and the ability for vasodilation. Endothelial dysfunction is an important pathophysiologic factor underlying both vasculogenic erectile dysfunction and atherosclerosis in other vascular beds(9). There's currently little data on the effectiveness of PRP for ED. Platelet Rich Plasma penile injection therapy is a new, regenerative treatment option for erectile dysfunction. In this study wecompare the effect of intracavernosal injection of platelet rich plasma with oral Phosphodiesterase type 5 inhibitors and intracavernosal injection of saline 0.9% (placebo effect) with oral Phosphodiesterase type 5 inhibitors on treatment of erectile dysfunction patients.

PATIENTS AND METHODS

2.1. Study Design and Settings

This study is a prospective randomized study, included patients diagnosed with ED in the period between January 2022 and December 2022.

2.2. Eligibility

Thirty-eight patients with erectile dysfunction were recruited according to inclusion and exclusion criteria. The inclusion criteria are patients with age ranges between 18-60 years and diagnosed with erectile dysfunction for more than 6 months. The exclusion criteria are patients with history of medical problems such as mental impairment, previous penile surgery, previous intracavenosal injection of vasoactive agents, previous history of priapism, Peyronie's disease and post traumatic erectile dysfunction.

2.3. Sample Size Calculation

Sample size was calculated from the following equation of dichotomous outcome for an independent sample was: -

$$n_i = \{p_1(1- p_1) + p_2 (1-p_2)\} (Z/E)^2$$

Where ni is the sample size required in each group. Z is the value from the standard normal distribution reflecting the confidence level that will be used (Z=1.36 for 85%), and E is the desired margin of error (15%). P1 and P2 are the proportion of successes in each comparison group which obtained from the previous studies.The result of the equation revealed that the sample size needed for study to get a significant result, was 38 patients diagnosed with erectile dysfunction.

2.4. Randomization

Simple Randomization of cases: 38 Patients was randomized using computerized system software in a ratio 1:1 into two groups, 19 patients in each group: group A intracavernosal injection of platelet rich plasma with oral PDE5Is and group B intracavernosal injection of saline 0.9% with oral PDE5Is.

2.5. Procedures

Preoperative:Patients were identified and detailed history such as personal history, sexual history, past history of medical disorders or operations, evaluation of erectile function using an International Index of Erectile Function (IIEF-5**)**(10).

The IIEF-5 score is the sum of the ordinal responses to the 5 items 22-25: No erectiledysfunction, 17-21: Mild erectile dysfunction, 12-16: Mild to moderate erectiledysfunction, 8-11: Moderate erectile dysfunction 5-7: Severe erectile dysfunction.

Physical examination and initial laboratory workup such as hormonal profile, lipid profile and blood sugar level (HbA1c) were performed. Also, routine laboratory workup was done.

2.5. Surgical Techniques

The two group were treated by daily Phosphodiesterase type 5 inhibitors (tadalafil 5 mg daily dose) for two months. Intracavernosal injection of 1 ml platelet rich plasma (platelet concentration = 1.0×10^6 plt/µL (11) and saline 0.9% (placebo) (1ml) was done once per week for 2 months.

1. ***Platelet rich plasma preparation: -***

Identify the blood sample with patient specific labels and attach two labels for the final preparation. Place the tubes in a sterile transfer box and proceed to cell preparation room. Centrifuge the tubes for 5 min at 1000 rpm at room temperature. Remove platelets with a sterile 5 ml pipette inserted above the buffy coat and transfer plasma and platelets to a new 5 ml Falcon centrifuge tube. Centrifuge the tube for 5 min at 3000 rpm at room temperature.

Keep the pellet with 1 ml plasma and transfer to an insulin syringe.

Close the syringe with a sterile cap and attach a patient label.

Transfer the final preparation in 1 syringe to a new transfer box and place a patient label on the outside before returning to patient.

Platelets are ready to use for injection (0.5 ml PRP concentrate in each corpus cavernosum).

2. ***Technique of intracavernosal injection:-***

Under compete aseptic condition; The intracavernosal injection was performed with 28- or 27-gauge needle. The contents of the syringe were gently and smoothly injected into the cavernous body (0.5 ml in each corpus cavernosum), at 3 o'clock and 9 o'clock positions at the proximal part of the shaft of penis. After injection, the needle and syringe were removed in a rapid fashion and compression was applied to the injection site for 1 to 2 minutes then massage of the penis was done for 2-3 minutes to distribute the platelet rich plasma in the whole penis.

2.6. Post-Operative Care

All patients were asked to follow up at outpatient clinic.

Follow- up:

1. All patients answered the Arabic version of IIEF-5 questionnaire (10)in structured interview before and 3 months after initiation of therapy.
2. Patients in both groups were followed up for the following outcomes: -
    a. Post ICI injection symptoms
        i. Pain
        ii. Edema
        iii. Priapism
    b. Any deviation of post injection course need for pharmacological treatment

2.7. Ethical Issues

This study was approved by the local Aswan Ethical committee. All patients were counseled and informed consent was obtained from each patient and goals and risks of this study were thoroughly explained.

2.8. Data management and Statistical analysis

The collected data was revised, coded, tabulated, and introduced to a PC using Microsoft excel. All statistical analysis were done using **SPSS version 25 (2017).** Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Results

The mean age ± SD in group A was 50 ± 10 years and in group B was 49 ± 9 years respectively(p value 0.7)

Regarding the co-morbidities, in group A 6 cases had HTN, and 11 cases had DM, while in group B 7 cases had HTN and 12 cases had DM.The study participants were categorized according to the international index of erectile function type 5 (ILEF-5) into mild ED, mild to moderate , moderate and severe ED.

There were 2 cases with mild ED in group A and 3 cases in group B. while there were 2 cases with mild to moderate ED in both groups. Also, both groups include 5 cases with moderate ED . as regard to severe ED there were 10 cases in group A and 9 cases in group B.

Table 2shows that after injection, 8 cases become with no Ed, moreover, the number of patients with mild ED, mild to Moderate, and moderate ED increased after injection in both groups. While number of severe ED reduced after injection.

After treatment of the two groups by daily Phosphodiesterase type 5 inhibitors (tadalafil 5 mg daily dose). Intracavernosal injection of platelet rich plasma for group A and saline 0.9% (placebo) for group B for two months the results were as the following:

There were 6 cases had no ED in group A and 2 cases had no ED in group B while there were 6 cases with mild ED in group A and 4 cases in group B. Moreover, there were 3 cases with mild to moderate ED in group A and 2 cases in group B. There were 2 cases with moderate ED in group A and 6 cases in group B . as regard to severe ED there were 2 cases in group A and 5 cases in group B.

Table 3shows that the mean ILEF-5 score after injection, in group A was 17.63 and in group B was 12.95.

The mean difference (4.684) showed to be statistically significant. (p-value < 0.05).
The study showed that the mean difference between mean ILEF-5 score before and after injection in group A was (-7.789) and it was statistically significant p-value < 0.001. meanwhile the mean difference between mean ILEF-5 score before and after injection in group B was (-3.053) and it was statistically significant p-value < 0.001.
The most common complication reported in this study was edema in which 7 cases (36.8%) in group A and 13 cases (68.4%) in group B (p-value>0.05). As regarding pain 5 cases (26.3%) were reported in group A compared to 14 cases (73.7%) were reported in group B (p-value< 0.01).
There were 5 cases had post injection pain in group A and 14 cases had post injection pain in group B , p value (0.01). Regarding post injection edema, there were 7 reported cases in group A while in group B there were 13 reported cases, P value (0.051). No cases had reported priapism or infection in either groups.

DISCUSSION

ED is defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance (12–14) .Diabetes, hypertension, cardiovascular disease, smoking, and obesity are the key risk factors for ED, which can be organic, psychogenic, or mixed.(15).These risk factors have a negative impact on NO activity in penile, vascular tissue, Endothelial dysfunction and decreased NO production or bioavailability have emerged as important pathophysiological processes in ED.(4).The most frequent underlying cause of organic male sexual dysfunction is certainly vascular insufficiency. (6). Although oral PDE5 inhibitors are generally an effective and well-tolerated therapy for ED, such therapies are still far from curing ED and do not reverse the vasculopathic or neuropathic processes associated with ED(16). Moreover, certain populations with organic ED, such as that resulting from diabetes or radical prostatectomy, respond poorly to PDE5 inhibitors. The degree of endothelial dysfunction or nerve injury may be associated to the lower response to PDE5 inhibitors(16).PRP is a platelet concentration in a little amount of plasma. Platelets' alfa granules contain growth factors such as platelet-derived growth factor, transforming growth factor-, and insulin-like growth factor-I, which, once released, may favorably affect wound healing.(17).
Platelets are growth factor storage pools for platelet-derived growth factor, transforming growth factor-ß, platelet-derived epidermal growth factor, vascular endothelial growth factor, insulin-like growth factor-1, fibroblastic growth factor, and epidermal growth factor. They also contain cytokines and many other proteins (18).
This work aimed to assess and compare the use of intracavernosal injection of PRP with oral PDE5 inhibitors versus oral PDE5 inhibitors alone for treatment of erectile dysfunction patients. Regrading to IIEF-5, before treatment there was no statistically significant difference between group A and group B. While after the intervention there was statistically significant difference between both groups. p-value< 0.05.Our results come in alignment with a double-blind RCT done by**poulios et al**(19) assessing the efficacy and safety of PRP injections alone in comparison to saline alone without PDE5 inhibitor. The study found that

PRP injection provide statistically significant improvement more than placebo after one month of injection, p-value < 0.01.

Angiogenesis is a feature of wound healing as well as other ischemia and inflammatory disorders. A wide range of pro- and anti-angiogenic chemicals has previously been identified. Because it is a highly selective mitogen for endothelial cells, VEGF is an intriguing inducer of angiogenesis and lymphangiogenesis. Signal transduction involves the interaction of tyrosine kinase receptors, which leads in endothelial cell proliferation, migration, and the creation of new vessels. (20). In the present study, there were 5 cases had post injection pain in group A and 14 cases had post injection pain in group B , p value (0.01). Regarding post injection edema, there were 7 reported cases in group A while in group B there were 13 reported cases, P value (0.051). These results were replicated by**An et al**(21). who said that Side-effects might appear from mild pain and occasional swelling to rarely infections. Before the start of therapy there were some concerns about possibility of cavernous fibrosis as platelets are the storage pools of growth factors transforming growth factor-ß and fibroblastic growth factor(18).TGF-β has been suggested as the most relevant fibrogenic cytokine (22,23).In our work, the presence of clinical improvement in our patients may suggest that the regenerative power of platelet rich plasma more profound than the fibrosis inducing effect caused by the same treatment. Moreover, the interaction between the different growth factors might have accompanied positive effect rather than the effect of each individual growth factor.In this study. Currently, there are many commercial systems available that differ in terms of speed of centrifugation, number of centrifugations, the use of anticoagulant, the presence of leukocytes in the preparation(24) .According to our knowledge, this is the first study to compare between ICI of PRP with oral PDE5 inhibitors and oral PDE5 inhibitors alone.

Limitation of the study include inability to extract some related patient demographics like smoking and obesity.Given the invasive nature of penile doppler, we didn't do routine penile duplex for all patients. The fact that the best technique of PRP preparation, number of injections, optimum duration of treatment, optimum dose needed are not yet standardized. Also, the long-term complications of this procedure are not yet established. The short time frame of our study (3 months) is one of the drawbacks of this study.

CONCLUSION

ICI of PRP with PDE5 inhibitors improve erectile function and patient satisfaction more than PDE5 inhibitors alone and might be an optional treatment for patients with erectile dysfunction.

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Conflict of Interest: The Authors declare that there is no conflict of interest.

Financial Disclosure

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Table 1: Demographic data of the included participants

		Group A N= 19	Group B N= 19	p-value
		Number (%)	Number (%)	
Age (Mean ± SD)		50 ± 10	49 ± 9	0.75
Co-morbidities:				
HTN		6 (31.6%)	7 (36.8%)	0.73
DM		11 (57.9%)	12 (63.2%)	0.74
IIEF-5 Categories before injection	Mild Erectile Dysfunction	2 (10.5 %)	3 (15.8%)	0.243
	Mild to Moderate Erectile Dysfunction	2 (10.5 %)	2 (10.5 %)	0.588
	Moderate Erectile Dysfunction	5 (26.3%)	5 (26.3%)	0.071
	Severe Erectile Dysfunction	10 (52.6%)	9 (47.4%)	0.639

Table 2: IIEF-5 categories before and after the injection by group

		Group A N= 19	Group B N= 19	p-value
		Number (%)	Number (%)	
IIEF-5 After injection	No Erectile Dysfunction	6 (31.6 %)	2 (10.5 %)	0.661
	Mild Erectile Dysfunction	6 (31.6 %)	4 (21.1%)	0.812
	Mild to Moderate Erectile Dysfunction	3 (15.8%)	2 (10.5 %)	0.842
	Moderate Erectile Dysfunction	2 (10.5 %)	6 (31.6 %)	0.236
	Severe Erectile Dysfunction	2 (10.5 %)	5 (26.3%)	0.354

Table 3: Comparison between Group A and group B in IIEF-5 before and after injection

	Group A	Group B	Mean difference [95% CI]	p-value
IIEF-5Before	9.84 ± 4.98	9.89 ± 5.03	-.053 [-3.347- 3.242]	0.864
IIEF-5 After	17.63 ± 5.45	12.95 ± 5.75	4.684 [0.995- 8.373]	0.014

Table 4: Comparison between each group over time.

	Mean IIEF-5 before	Mean IIEF-5 after	Mean difference. [95% CI]	p-value
Group A	9.84 ± 4.98	17.63 ± 5.45	-7.789 [-10.036 , -5.543]	< 0.001
Group B	9.89 + 5.03	12.95 + 5.75	-3.053 [-4.312 , -1.793]	< 0.001

Table5. complications and need for medication.

Complications	**Group A N= 19 Number (%)**	**Group B N= 19 Number (%)**	**P value**
Pain	5 (26.3%)	14 (73.7%)	0.01
Edema	7 (36.8%)	13 (68.4%)	0.051
Priapism	0 (0%)	0 (0%)	-
Infection	0 (0%)	0 (0%)	-
Needs for medication	3 (15.8%)	2 (10.5%)	0.63

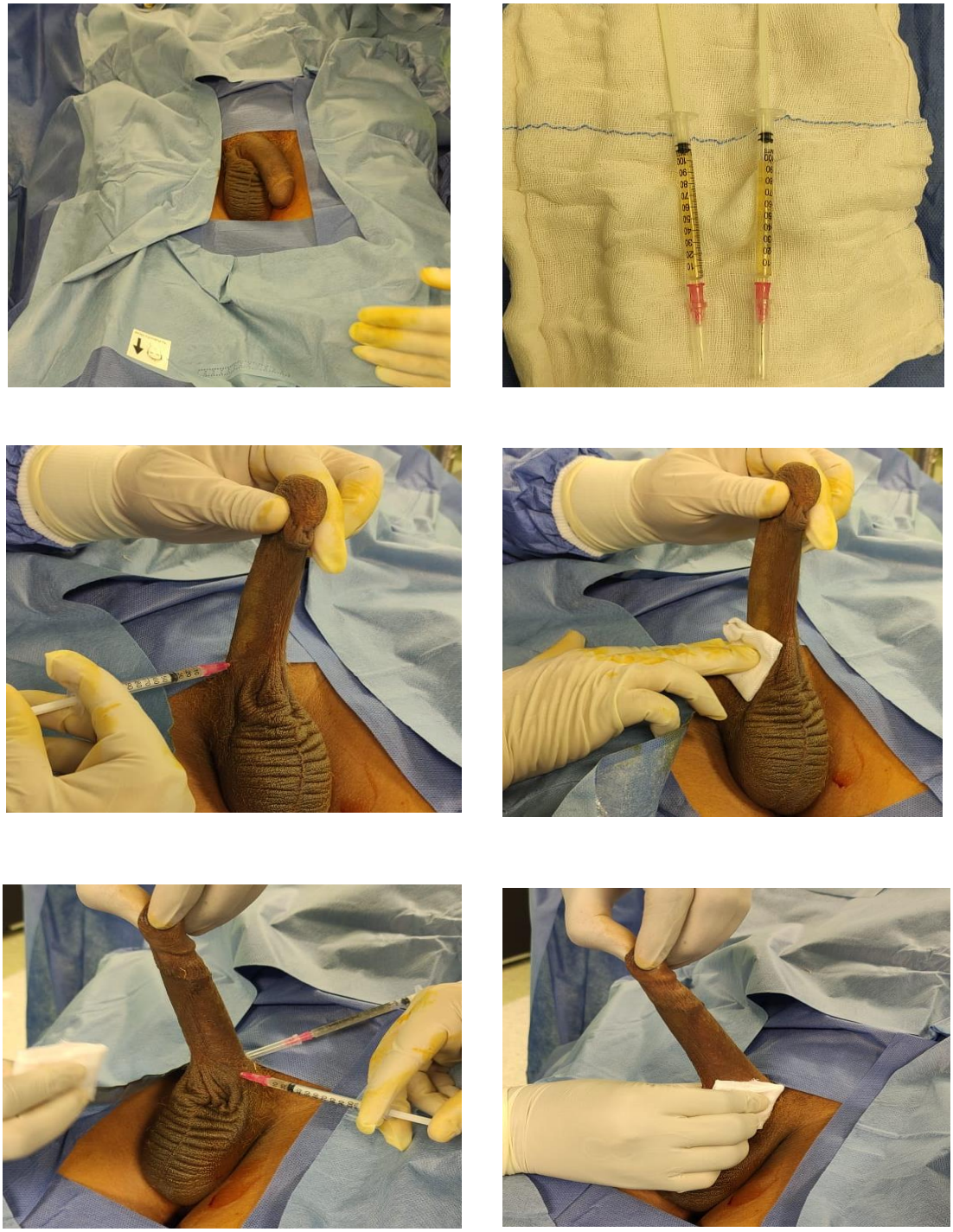

Figure 1:Steps of PRP injection

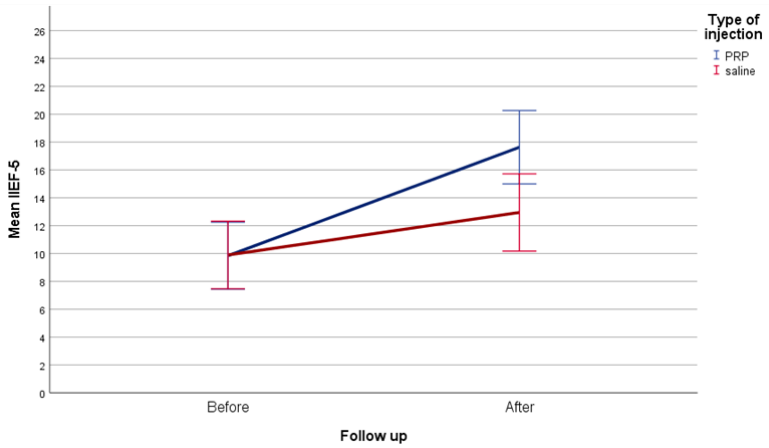

Figure 2:IIEF-5 pre and post treatment