Al-Nasser R, et al., J Reprod Med Gynecol Obstet 2018, 3: 011
DOI: 10.24966/RMGO-2574/100011

HSOA Journal of Reproductive Medicine, Gynaecology & Obstetrics

Review Article

The Effectiveness of Autologous Platelet-Rich Plasma (PRP) in the Therapy of Infertile Men with Non-Abstractive Azoospermia

Rami Al-Nasser*, Zakwan Khrait* and Samer Jamali

British-Syrian IVF & Fetal Medicine Centre, Al-Rasheed Hospital, Damascus, Syria

Abstract

Introduction: Non-obstructive azoospermia is a cause of male infertility and despite the advancement in gynecology it is still one of the most challenging conditions to treat. One of the possible treatments for this condition may be Platelet-Rich-Plasma (PRP) due to its well-known regenerative potential.

Objectives: To evaluate the effectiveness of autologous PRP in the therapy of infertile men with nonobstructive Azoospermia.

Methods: Seventy-one patients received ½ ml PRP in each testicle which was prepared by centrifuging patient's own blood. FNA parameters and FSH levels of the patients were measured before and after the procedure. Testosterone level was measured before the procedure. All the required data for the study was collected retrospectively from the hospital records.

Results: A couple of NOA cases developed normal spermatogenesis. Post-procedure FSH was higher than preprocedural FSH (MD 1.737, p .560). Patients with spermatocytes in the initial FNA report showed a lower percentage of azoospermia than their counterparts (11.4% vs 44.4%).

Conclusion: Numerous studies have proven PRP to have a statistically significant level of regenerative potential in different branches of medicine. PRP therapy has been successful for the treatment of some causes of female infertility. The treatment potential of PRP for male infertility may not be underestimated.

***Corresponding author:** Rami Al-Nasser, British-Syrian IVF & Fetal Medicine Centre, Al-Rasheed Hospital, Damascus, Syria, Tel: +963 932550992; Email: raminasser03@yahoo.com

Zakwan Khrait, British-Syrian IVF & Fetal Medicine Centre, Al-Rasheed Hospital, Damascus, Syria, Tel: +971 555242644; Email: zakwankhrait@hotmail.com

Citation: Al-Nasser R, Khrait Z, Jamali S (2018) The Effectiveness of Autologous Platelet-Rich Plasma (PRP) in the Therapy of Infertile Men with Non-Abstractive Azoospermia. J Reprod Med Gynecol Obstet 3: 011.

Received: August 02, 2018; **Accepted:** August 31, 2018; **Published:** September 14, 2018

Introduction

Platelet Rich Plasma (PRP), also known as autologous platelet gel, Plasma Rich in Growth Factors (PRGF) and Platelet Concentrate (PC), is a high concentration of autologous platelets suspended in a small volume of plasma after centrifugation [1]. More than 800 types of protein molecules, cytokines, hormones and chemo-attractants are carried by the platelets [2]. When platelets get activated, numerous biologically active proteins that stimulate cell proliferation, growth and differentiation are released. Activated platelets also release various types of growth factors like Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor β (TGF-β), Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), Insulin like Growth Factor (IGF-1) and Hepatocyte Growth Factor (HGF) [3].

Platelet Rich Plasma (PRP), with its rich growth factor composition, has been already proven beneficial in regenerative therapy [4]. Some of the specific beneficial effects of PRP are accelerated angiogenesis and anabolism, inflammation control, cell migration, differentiation and proliferation were identified by a few previous studies [5-7]. As a result, PRP is nowadays used in various clinical scenarios that required improved tissue regeneration in maxillofacial surgery, neurobiology, orthopedics, sports medicine and ophthalmology [3,8,9]. Potential benefits of PRP have also been studied in the field of gynecology; a study revealed PRP can increase endometrial thickness and improve the pregnancy outcome with thin endometrium [9]. According to Colombo GVL, PRP has the potential to reduce the implantation failures by increasing the expression of adhesion molecules, ovarian rejuvenation and folliculogenesis reactivation in peri-menopausal women [2,10]. PRP can improve the structural and functional impairment of the testis.

Male factor causes approximately 30% to 50% of infertile couples. Non-Obstructive Azoospermia (NOA) is a failure of spermatogenesis within the testis [11]. In the past, males with Non-Obstructive Azoospermia (NOA) had no therapeutic options outside of assisted reproductive techniques to conceive a biological child. These patients were bound to rely on options of donor sperm or adoption [12]. Then several sources had suggested about hormonal therapies and stem cell therapy for NOA [11,13]. Till date, no human study was done to identify potential benefits of PRP in NOA treatment. Given all the aforementioned positive outcomes of PRP therapy in various medical fields, little is known regarding the application of PRP in the testicular injection. In our current study, we aim to know the potential benefit of autologous PRP therapy of infertile men with Non-Obstructive Azoospermia (NOA), if so we try to select the criteria of PRP in (NOA) patients.

Material and Methods

Sample size: 71

Study design: Retrospective chart-review study

Platelet-Rich Plasma (PRP) is prepared from fresh whole blood which is collected from a peripheral vein, stored in Acid Citrate Dextrose solution A (ACD-A) anticoagulant and processed to increase platelets by separating various components of blood, hence the injected fluid prepared from autologous blood by centrifugation using Dr. PRP kits and equipment (USA). Consent form was given and signed.

Under sedation men had been undergone PRP intra-testicular injection with ½ ml in each testicle using fine needle, the injections were repeated to those who have more than one failed TESE previously with no mature sperm where found.

Male factor causes approximately 30% to 50% of infertile couples. The Azoospermia diagnosis of referral patients or outpatients have been established on the basis of, at least, two semen analysis evaluation done at separated occasions, if no spermatozoa are observed in the wet preparation, we followed the World Health Organization (WHO) recommendations as to perform an examination of the centrifuged sample (300 X g or greater for 15 minutes), followed by detailed history taking including general health, libido, sexual health, past fertility, sexual activity and previous exposure to surgery, drugs, mumps infection, irradiation and physical examination. Physical examination includes genital and local examination for detection of signs of Klinefelter syndrome, testicular atrophy, absence of vas and investigations includes FSH and Testosterone while some other hormones which may influence the spermatogenesis procedure e.g., Estradiol and Prolactin not included in this study but focused on FSH and Testosterone level. 2-4 months following PRP, the TESA (Testicular Sperm Aspiration) was performed after confirmed semen analysis azoospermia was performed shortly prior to second TESA.

Statistical Analysis

The categorical variables were presented as frequencies and percentages and continuous variables were presented as mean ± standard deviations. The statistical difference between the initial FSH and post procedure FSH for all patients and for patients with primary & secondary spermatocytes in their initial FNA reports were calculated by paired samples t-tests. The analysis was performed in 95% confidence interval using Statistical Package for Social Science (SPSS), version 23 (IBM, Armonk, NY, USA).

Results

Total 91 patients were included in this study. The mean ± SD age of all respondents was 37.60 ± 6.66 years. The summary of initial FNA/SA parameters of all patients were as following: primary and secondary spermatocytes in 54.9% cases, no sperm & no spermatogenesis in 24.2% cases, few motile and few immotile sperms in 14.3% cases, oligospermia in 3.3% cases and other conditions in 3.3% (e.g., rare sperm in sample, Kartagener syndrome etc.,) cases. The mean ± SD FSH level of all patients before PRP therapy was 22.89 ± 13.12 IU/ml and after PRP was 24.56 ± 23.43 IU/ml. The mean ± SD level of testosterone was 571.08 ± 844.72 ng/dL. Thirty (33.0%) patients received Letrazole. The summary of final FNA report of all patients were: primary & secondary spermatogenesis in 18.7% cases, no sperm & no spermatogenesis in 22.0% cases, few motile & few immotile sperms in 29.7% cases, oligospermia in 2.2% cases normal sperm in 2.2% cases and missing data for 25.3% cases (Table 1).

Parameters	N (%)/mean ± SD
Age in years	37.60 ± 6.66
Initial FNA/ SA parameters	
Primary & secondary spermatocytes	50 (54.9)
No sperm and no spermatogenesis	22 (24.2)
Few motile and few immotile sperms	13 (14.3)
Oligospermia	3 (3.3)
Other	3 (3.3)
Initial FSH	22.89 ± 13.12
Testosterone level (ng/dL)	571.08 ± 844.72
Protocol	
No treatment	61 (67.0)
Letrazole	30 (33.0)
Final FNA report	
Primary & secondary spermatocytes	17 (18.7)
No sperm and no spermatogenesis	20 (22.0)
Few motile & few immotile sperms	27 (29.7)
Oligospermia	2 (2.2)
Normal sperm	2 (2.2)
Missing	23 (25.3)
Final FSH	24.56 ± 23.43

Table 1: Distribution of all patients by age, initial & final FNA report, initial & final FSH, testosterone level, and protocol (n = 91).

Figure 1 shows the percentages of 'no sperm and no spermatogenesis', 'few motile & few immotile' and 'normal sperm' in final FNA reports for patients with primary & secondary spermatocytes prior to PRP therapy (n = 50) and patients with no primary & secondary spermatocytes prior to PRP therapy (n = 41). Although slight increase of FSH was observed after PRP therapy in all patients, the level of increase was not statistically significant (95% CI 4.185-7.660, p .560). When only the patients with primary & secondary spermatocytes were taken in the analysis we still didn't find and statistically significant increase in final FSH level compared to their initial FSH levels (95% CI 7.899-3.323, p .412) (Table 2).

Discussion

In the current study, we have observed 2 cases with the restoration of normal functioning testes after PRP therapy. A former mice study reported Morpho-functional restoration of mice testes following doxorubicin hydrochloride exposure. The same study has also reported testes mice treated with PRP showed improvement of the testicular function at histological level [14]. PRP has been proven safe and effective for treating many urological conditions as well, for example erectile dysfunction, Peyronie's disease and stress urinary condition [15]. According to Bir et al., Battinelli et al., Sanchez-Gonzalez et al., the regenerative potential of platelet rich plasma comes from the growth factors released by the platelets [16-18].

We have observed FSH level to increase after PRP therapy in the current study. The present study also showed the cases who had primary and secondary spermatogenesis prior to PRP therapy had a

lower percentage (11.4%) of azoospermia compared to their counterparts (44.4%). PRP therapy have proliferative effects on endometrium and ultimately increase implantation rate and reduce female fertility [9]. As per the male infertile we have observed improvement in terms of hormonal level and spermatogenesis in the current study. In the current study, we did not observe any deteriorating effect of PRP therapy.

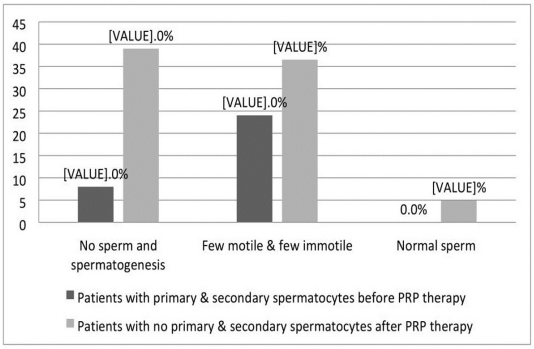

Figure 1: The following chart is showing the percentages of 'no sperm and no spermatogenesis', 'few motile & few immotile' and 'normal sperm' in final FNA reports for patients with primary & secondary spermatocytes prior to PRP therapy (n = 50) and patients with no primary & secondary spermatocytes prior to PRP therapy (n = 41).

	Mean	SD	95%CI	t	p-value
Initial FSH - final FSH (in all cases, n=71)	-1.737	±24.280	4.185-7.660	0.586	0.560
Initial FSH - final FSH (in patients with primary & secondary spermatocytes before PRP therapy, n=35)	2.288	±15.825	7.899-3.323	0.831	0.412

Table 2: Paired samples t-test to find out the difference between initial FSH and final FSH for all patients (n = 71) and for patient with primary & secondary spermatocytes before PRP therapy (n = 33).

Conclusion

The excellent regenerative potential of PRP has been reported by various studies. And the therapy doesn't cause any major complications because PRP is prepared from patient's own blood. We had some limitations in our current study hence the beneficial effects of PRP for the treatment of nonobstructive azoospermia could not be proven at a statistically significant level. But PRP therapy still may have a great potential for the treatment of male infertility and increases spermatogenesis. The current study may act as a foundation for future large-scale, multicenter randomized control trials.

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