Int J Fertil Steril
International Journal of Fertility & Sterility
Homepage: https://www.ijfs.ir/
Original Article
Vol 18, Suppl 1, Spring 2024, Pages: 71-76

Effects of Testicular Platelet-Rich Plasma Injection on Sperm Parameters in Men with Severe Oligoasthenoteratozoospermia: A Clinical Trial Evaluation

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Abstract

Background: Severe oligoasthenoteratozoospermia (OAT), characterized by a reduced sperm count, motility, and altered morphology, presents a significant challenge in the field of male infertility. Platelet-rich plasma (PRP), renowned for its regenerative capabilities, emerges as a potential intervention for this condition. This study aims to explore the impact of PRP on male infertility, focusing specifically on individuals with severe OAT.

Materials and Methods: The clinical trial study involved 88 infertile men diagnosed with OAT and devoid of underlying diseases. These participants were referred to the infertility center and subsequently divided into two cohorts: a control (44 individuals) and an intervention group (44 individuals). Patients in the intervention group received 2 cc of PRP in each testicle, prepared by centrifuging the patients autologous blood samples. Sperm parameters and DNA fragmentation index (DFI) of the patients were measured before and after the procedure. Statistical analysis used SPSS version 16 software, with a significance level set at less than 5%.

Results: The statistical analysis revealed a significant difference in concentration (11.32 ± 8.44 vs. 16.06 ± 15.16, P=0.030), progressive motility (8.86 ± 7.79 vs. 11.97 ± 11.82%, P=0.014) and DNA fragmentation (25.62 ± 12.84 vs. 17.23 ± 9.15%, P<0.001) between the control and intervention groups after PRP injection. However, no significant difference was found in normal morphology (1.63 ± 1.44 vs. 1.81 ± 3.68%, P=0.628) and volume (2.13 ± 0.82 vs. 2.24 ± 1.43, P=0.663) between the control and intervention groups after PRP injection.

Conclusion: This study demonstrates the effectiveness of PRP treatment in increasing sperm concentration and motility, while also reducing sperm DNA fragmentation. However, further studies are needed to validate these findings (registration number: IRCT20220317054318N2).

Keywords: Asthenospermia, Male Infertility, Oligospermia, Platelet-Rich Plasma, Teratospermia

Citation: Fazli F, Torkashvand H, Soltanian AR, Babalhavaeji A, Olomi H, Pilehvari Sh. Effects of testicular platelet-rich plasma injection on sperm parameters in men with severe oligoasthenoteratozoospermia: a clinical trial evaluation. Int J Fertil Steril. 2024; 18 Suppl 1: 71-76, doi: 10.22074/IJFS.2024.2011066.1535

Introduction

The term "infertility" refers to the condition in which a couple is unable to achieve conception even after consistently having unprotected sexual intercourse for one year (1). Estimates by the World Health Organization and epidemiological studies show that the worldwide prevalence of infertility is about 17.5% (2). Developing countries, in particular, bear a substantial burden, with one in every six couples grappling with infertility (3). Remarkably, half of the instances of infertility in couples can be attributed to male factors (4). These factors span a spectrum, ranging from genetic conditions like Klinefelter's syndrome (5) to environmental influences such as exposure to contaminants like mercury, arsenic, and lead (6), all of which can significantly impact male fertility. Infections such as human immunodeficiency virus (HIV), human papillomavirus (HPV), cytomegalovirus (CMV), adenoviruses, parvovirus, and mumps (7), coupled with lifestyle choices and other environmental factors, contribute to the multifaceted landscape of male

Received: 07/September/2023, Revised: 17/December/2023, Accepted: 09/January/2024
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Royan Institute
International Journal of Fertility & Sterility

infertility. Male infertility typically refers to a condition in which the inability to conceive is associated with a specific alteration found in the male partner. Possible consequences of this change include a sperm concentration below the lower reference (<15 million sperm/mL) in ejaculate (oligozoospermia), reduced or absent sperm motility (<32%) in fresh ejaculate (asthenozoospermia), and abnormal sperm morphology (teratozoospermia). However, a combination of these factors is generally regarded as oligoasthenoteratozoospermia (OAT) (8). Regrettably, the majority of instances of severe OAT are attributed to an unexplained testicular abnormality or disorder (9). As a result, rational therapeutic approaches have not been pursued. Instead, infertile men have been prescribed numerous uncontrolled treatments without sufficient pathophysiological justification or solely based on empirical evidence.

Based on innovative medical approaches, the use of platelet-rich plasma (PRP), which is a high concentration of autologous platelets suspended in a small amount of plasma after centrifugation, appears to be a safe and high-potential therapeutic option (10-12). Due to its abundant growth factor content, PRP has already demonstrated its advantages in the field of regenerative therapy (13). Certain advantageous effects of PRP, such as accelerated angiogenesis, inflammation control, cell migration, differentiation, and proliferation, have been highlighted in several earlier research studies (14-16). Currently, PRP is increasingly utilized in the field of reproductive medicine, owing to its regenerative potential. Extensive research has explored the potential benefits of PRP in female reproductive medicine, with studies focusing on intrauterine PRP injections for patients with recurrent implantation failure (RIF) (17) and intraovarian PRP applications for women with poor ovarian response (POR) (18). In contrast, the investigation of PRP's effects on male infertility is still in its nascent stage. Some studies have examined its potential in this context, including its impact on the fertility of individuals with non-obstructed azoospermia (19). However, it is crucial to acknowledge that the existing scientific evidence is not yet sufficient to establish definitive conclusions.

To the best of our knowledge, there is a scarcity of studies exploring the impact of PRP on male infertility, especially in the context of a focused investigation on severe OAT. This study aims to fill this research gap by investigating the specific impact of PRP on male infertility, with a focus on improving sperm parameters in individuals with severe OAT. Through these efforts, our study seeks to contribute to the advancement of regenerative therapies in the field of reproductive health.

Material and Method

The present study is a randomized clinical trial conducted at the Infertility Center of Fatemieh Hospital in Hamedan from January 2022 to August 2023. Before participating in the study, each participant provided informed consent, expressing their willingness to take part in the clinical trial. Comprehensive information about the research, including its purpose, procedures, and potential risks and benefits, was conveyed through verbal explanations and written documents. Emphasis was placed on voluntary participation, ensuring participants' right to withdraw at any stage without consequences. Opportunities for questions and clarification were provided prior to obtaining formal consent through signed forms. The trial was documented in the Iran Registry of Clinical Trials (IRCT20220317054318N2). The Ethical Committee of Hamedan University of Medical Sciences granted approval for the implementation of the study (IR.UMSHA.REC. 1401.946).

Patients selection

Eighty-eight infertile males, who had been referred to the infertility center of Fatemieh Hospital for infertility treatment, were enrolled in this clinical trial according to the sample size calculation formula. Participants were recruited from those referred to the infertility center for infertility treatment, aiming to enhance the study's relevance to a broader population seeking infertility care. The inclusion criteria were having an age range of 20-45 years old with severe OAT (the sperm count $\leq 4\times10^6$ /ml, progressive motility sperm ≤30%, morphologically normal sperm ≤1%), not receiving other treatments such as hormone therapy, not having underlying diseases (such as diabetes, kidney, liver diseases, addiction to drugs and alcohol), cancer, and receiving chemotherapy treatments.

Experimental design

In the present study, 88 infertile male patients were divided into two groups: control (n=44) and intervention (n=44). Semen samples were analyzed before PRP injection in both groups. In the intervention group, a urologist injected PRP into the testicular tissue using local anesthesia, with the amount of PRP varied from 1 to 2 cc depending on the size of the testicle. After three months, another semen sample was taken from the same individuals for sperm analysis and DNA fragment index evaluation. There was no intervention in the control group.

The sperm sample is collected after abstaining from sexual activity for three days. The diagnosis of OAT was verified by conducting two spermiogram tests one month after the initial examination, and if there is a difference of more than 20% between the samples, a third test is performed.

In this study, the semen sample was incubated for 30 minutes at a temperature of 37°C to transform it from a coagulated form to a liquefied state.

Platelet-rich plasma preparation

The PRP was prepared using their autologous blood samples following established standard techniques (20). Briefly, 5 cc of whole blood was collected in tubes containing anticoagulant (EDTA) and gently mixed to prevent clotting. The blood was then centrifuged at 3000

rpm for 5 minutes, separating into distinct layers. Red blood cells settled at the bottom, a middle layer known as the buffy coat containing white blood cells and platelets, and plasma at the top.

Using a sterile pipette or syringe, the upper layer (plasma) was carefully transferred to a new, sterile tube. This plasma was then centrifuged at 3500 rpm for 15 minutes. The upper two-thirds, consisting of PPP, were removed, leaving the lower one-third containing PRP.

To activate the PRP, 23 microliters of 10% calcium chloride were added, followed by incubation at 37°C for 15 minutes. After incubation, the tube was centrifuged for 10 minutes at 4000 rpm to obtain activated PRP.

The analysis of sperm parameters

The assessment of volume, sperm concentrations, motility, and morphology was carried out following the laboratory manual from the World Health Organization (WHO) (21).

Semen analysis

The most accurate way to determine the volume is by measuring the sample within the receptacle in which it is collected. Collect the sample in a pre-measured single-use receptacle, then measure the combined weight of the receptacle containing the seminal fluid. Subtract the weight of the receptacle to obtain the net volume (21).

Sperm counts were conducted by observing spermatozoa under a microscope using the improved Neubauer hemocytometer (Neubauer IMPROVED, Marienfeld, Germany). Sperm concentrations were calculated in accordance with the protocols outlined in the WHO laboratory manual (21).

The 5th edition of the WHO classifies sperm motility into three categories: progressive, nonprogressive, and immotile. A lower reference value of 32% is considered for progressive mobility, according to the WHO directive. For the evaluation of motility, 10 µL of liquefied sample is loaded into a clean glass slide previously maintained at 37°C, and then covered with a 22×22 mm coverslip. The prepared sample was positioned on the microscope's heating stage set to 37°C, and it was promptly assessed under a magnification of 400× (21).

Diff-Quik staining (MICROPTIC S.L. Co., Barcelona, Spain) was employed to assess the impact of PRP on sperm morphology. The procedures were carried out following the instructions provided in the kit. Around 10 µl of spermatozoa was spread onto a clean glass slide to create a thin and even layer, which was then air-dried at room temperature for a minimum of 10 minutes. The slides were stained using the recommended staining procedure outlined in the manual and examined using a brightfield microscope. Typically, of 200 spermatozoa per sample were categorized based on their morphology, and the overall number of abnormal spermatozoa was reported as a percentage (22).

Evaluation of DNA fragmentation

The evaluation of DNA fragmentation proportion was conducted using the Halo Sperm Kit (Halo kit, Idehvarzan Farda Company, Tehran, Iran). Initially, 50 µL of the samples were gently combined with preheated agarose gel obtained from the kit, and subsequently, 20 µL were positioned onto the previously coated glass slide. A 22×22 mm coverslip was then laid over the slide, which was then kept at a temperature of 4°C for 5 minutes. Following this interval, the coverslip was removed, and the slide was immersed in solution A (denaturing solution) for 7 minutes, followed by solution B (lysing solution) for 15 minutes at ambient temperature. The slide was rinsed using distilled water for an additional 5 minutes, then subjected to dehydration through progressively increasing concentrations of ethanol (70, 90, 100%). Upon complete drying, the slides were stained using the solution provided in the kit, encompassing components C, D, and E, for respective durations of 75 seconds, 3 minutes, and 2 minutes, respectively. After the staining process, a total of 200 spermatozoa were evaluated using a light microscope (1000×). The presence and size of halos generated under the light microscope were indicative of DNA fragmentation. Spermatozoa devoid of DNA fragmentation exhibited sizable or moderate halos, while spermatozoa exhibiting fragmentation displayed minimal or absent halos (23).

Statistical analysis

Quantitative clinical characteristics were described as mean ± SD. In this study, clinical characteristics were measured after the intervention. Mann-Whitney-U test was used to compare the initial clinical characteristics in the control and intervention groups. ANCOVA analysis was used to compare the outcomes after intervention, adjusting for the initial measures of each variable and covariates such as age, body mass index, duration of marriage, and duration of infertility. The significance level was set at less than 0.05, and data description and analysis were performed using SPSS software for Windows (version 16.0. Chicago, SPSS inc).

Result

Effect of platelet-rich plasma on sperm parameters

The effects of PRP on sperm parameters are presented in Table 1 and Figure 1. The evaluation of sperm concentration in the control group revealed a significant decrease in the compared to average sperm concentration following PRP injection in intervention group: 11.32 ± 8.44 vs. 16.06 ± 15.16, P=0.030. The rate of progressive sperm motility in the analysis of the control group was 8.86 ± 7.79%. Furthermore, the rate of progressive sperm motility was 85.03 ± 9.64% in the intervention group. The evaluation of sperm progressive motility in the studied groups revealed a notable rise in the average progressive

motility of sperm after PRP injection compared to the control group (P=0.014). The assessment of sperm morphology revealed that the proportion of normal sperm morphology in the control group was 1.63 ± 1.44%. In contrast, the intervention group resulted in 1.81 ± 3.68% normal morphology. However, no significant difference was observed in normal morphology (P=0.628). The assessment of sperm morphology revealed that the proportion of normal sperm morphology in the control group was 1.63 ± 1.44%. In contrast, the intervention group resulted in 1.81 ± 3.68% normal morphology. However, no significant difference was observed in normal morphology. However, no significant difference was observed in normal morphology (P=0.628). The evaluation of sperm volume also showed that there was no significant difference between the control (2.13 ± 0.82) and intervention (2.24 ± 1.43) groups after PRP injection (P=0.663).

Table 1: Comparison of sperm parameters and DFI between control (n=44) and intervention (n=44), after the test

Indexes	Group	Mean ± SD	ST
Concentration sperm	Control	11.32 ± 8.44	F=4.86, P=0.030*
	Intervention	16.06 ± 15.16	
Morphology sperm	Control	1.63 ± 1.44	F=0.23, P=0.628
	Intervention	1.81 ± 3.68	
Motility sperm	Control	8.86 ± 7.79	F=6.28, P=0.014*
	Intervention	11.97 ± 11.82	
Volume sperm	Control	2.13 ± 0.82	F=0.19, P=0.663
	Intervention	2.24 ± 1.43	
DFI	Control	25.62 ± 12.84	F=20.32, P<0.001*
	Intervention	17.23 ± 9.15	

P value; The difference between control groups and intervention group. The significance threshold was deemed to be P<0.05. The P value is determined by ANCOVA model. DFI; DNA fragmentation index, SD; Standard deviation, and ST; Statistical test.

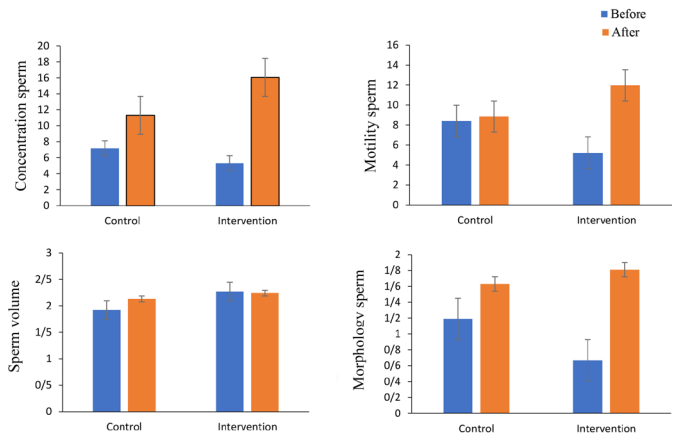

Fig.1: Comparison of sperm parameters in two control and intervention groups before and after the test.

Effect of platelet-rich plasma on DNA fragmentation status

The effects of PRP on sperm DNA fragmentation are presented in Table 1 and Figure 2. The percentage of sperm containing DNA fragmentation in the intervention group (17.23 ± 9.15%) was significantly lower than that in the control group (25.62 ± 12.84%, P<0.001).

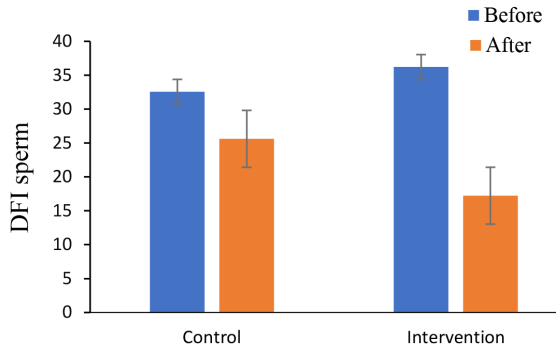

Fig.2: Comparison of DFI in two control and intervention groups prior to and after the test. DFI; DNA fragmentation index.

Discussion

The present study aimed to investigate the effects of testicular PRP injection on sperm parameters in men with severe OAT. The results of this study demonstrated significant improvements in sperm concentration, progressive motility, and DFI after PRP injection.

The statistical analysis revealed a significant difference in sperm concentration and progressive motility between the control and intervention groups after PRP injection. These findings suggest that PRP treatment can improve sperm parameters in men with severe OAT. The increase in sperm concentration and motility is particularly noteworthy, as these factors are crucial for successful fertilization and pregnancy. Concordant with our findings, Somova et al. (24) conducted a study aligning with our research focus. They observed that PRP injection in individuals with severe OAT led to improved sperm concentration and motility after 4 months, compared to those who did not receive PRP injection. Another important finding of this study is the significant reduction in DNA fragmentation observed in the intervention group after PRP injection. DNA fragmentation is known to have a negative impact on sperm quality and fertility potential. The decrease in DFI suggests that PRP treatment may help improve sperm DNA integrity, which is essential for successful embryo development and pregnancy. The improvement of sperm parameters observed in this study could be attributed to the growth factors present in PRP. PRP contains various growth factors, such as platelet-derived growth factor (PDGF) (25), transforming growth factor-beta (TGF-β) (26), insulin-like growth factor (IGF) (27), Fibroblast growth factor (FGF) (28), and vascular endothelial growth factor (VEGF) (29), among others. These growth factors have regenerative and reparative properties, which can potentially enhance sperm production, motility, and DNA integrity.

Numerous research studies have underscored the crucial role of Brain-derived neurotrophic factor (BDNF) in the

male reproductive system (30), with its receptor being identified within sperm (31). BDNF actively participates in initiating the phosphatidylinositol 3 kinase (PI3K) pathway, potentially serving a vital function in enhancing sperm motility and upholding DNA integrity through this specific pathway (32). As a result, any abnormalities in the expression of the BDNF gene might be closely associated with the onset of male infertility disorders. Moreover, the expression level of BDNF in seminal fluid samples obtained from men with oligoasthenospermia is notably lower when compared to samples from infertile men (33).

VEGF plays a crucial role as a polypeptide in the process of angiogenesis. The presence of both VEGF and its receptors within the male reproductive system has been substantiated, with the VEGF protein notably detected in spermatids, seminal plasma, Sertoli, and Leydig cells (34). In a study conducted by Iyibozkurt et al. (29), it was shown that VEGF has a beneficial effect on sperm motility and linear velocity.

Past research has showcased the existence of IGF-I within human samples, spanning across the testis, germ cells, and seminal plasma (35, 36). Additionally, a connection has been established between the levels of IGF-I in seminal plasma and the quality of semen (35). This underscores the notion that IGF-I potentially bolsters sperm motility through various mechanisms (37). Furthermore, it is plausible that IGF-2 might contribute to a substantial reduction in sperm DNA fragmentation (38). Hence, the amalgamation of these factors within PRP stands poised to exert a noteworthy influence on ameliorating sperm parameters and, consequently, on addressing male infertility through the utilization of different molecular mechanisms.

It is worth noting that no significant differences were observed in normal morphology and volume between the control and intervention groups after PRP injection. Although these parameters did not show significant improvements, they remain crucial factors to consider in the evaluation of male fertility. Further research is needed to explore the effects of PRP on these parameters and to determine the long-term effects of PRP treatment on male fertility outcomes.

The study's revelations regarding the potential of PRP in ameliorating sperm parameters in men with severe OAT carry substantial implications for both future research and clinical practice. While recognizing the necessity for further investigation to validate these findings and unveil the underlying mechanisms of PRP's impact on sperm parameters, the study prompts a call for more in-depth exploration. Future studies can probe into the intricate molecular pathways and growth factors involved in the enhancement of sperm parameters following PRP injection. Additionally, the research underscores the importance of ascertaining the long-term effects of PRP treatment on male fertility outcomes. Subsequent research endeavors may focus on evaluating the sustained impact of PRP on sperm parameters and DNA integrity over an extended period, with longitudinal studies offering valuable insights into the durability of the observed improvements.

In terms of clinical implications, the study lends support to the idea that PRP holds promise as a safe and effective therapeutic option for men with severe OAT. This suggests that PRP treatment could emerge as a compelling alternative to conventional approaches like hormone therapy or assisted reproductive techniques. Practicing clinicians may consider integrating PRP into the treatment repertoire for male infertility, especially in cases of severe OAT. Furthermore, PRP treatment provides a non-invasive and autologous avenue to enhance sperm parameters and DNA integrity. This facet carries significant clinical implications, offering a less invasive option for male infertility treatment. Clinicians and patients alike may find this approach appealing due to its potential to improve fertility outcomes without necessitating more invasive procedures.

Conclusion

The results of this study suggest that testicular PRP injection can improve sperm concentration, progressive motility, and DNA integrity in men with severe OAT. These findings support the potential of PRP as a safe and effective therapeutic option for male infertility. Further research is warranted to confirm these findings and to elucidate the underlying mechanisms of PRP's effects on sperm parameters.

Acknowledgments

The authors express their gratitude for the generous permission granted by the patients, allowing the utilization of their medical information in this study. There is no financial support and conflict of interest in this study.

Authors' Contributions

F.F., H.T.; Conceptualization and Methodology. H.T., A.B., H.O.; Data curation, Writing-original draft preparation, and Supervision. A.R.S.; Data collection, Classification, and Formal analysis. F.F., Sh.P.; Resources. H.T., Sh.P.; Writing- Reviewing and Editing. All authors read and approved the final manuscript.

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