

Journal of Regenerative Medicine & Biology Research

Research Article

Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study

Melissa M Rubio^{1*}

¹Principal Investigator for Research/Nurse Practitioner, H-Cyte, Texas, USA

*Corresponding Author: Melissa M Rubio, Principal Investigator for Research/Nurse Practitioner, H-Cyte, Texas, USA; Email: mrubiophd@outlook.com

Received Date: 20-05-2021; Accepted Date: 17-06-2021; Published Date: 25-06-2021

Copyright[©] **2021** by Rubio MM et al. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Abstract

Objective: Current management of Chronic Obstructive Pulmonary Disease (COPD) is aimed at improving symptoms and preventing exacerbations, yet those treatments cannot alter the natural progression of lung function decline over time. Autologous cellular therapy with PRP-PC may help prevent decline and improve quality of life among these patients.

Methods: 419 participants with COPD enrolled in this study underwent autologous cellular therapy with PRP-PC and outcomes measures assessed over the course of a year. Lung function with spirometry and breathing-related quality of life was assessed on all patients at baseline. Quality of life was re-assessed on all participants after 3, 6 and 12 months by phone and 150 participants returned for repeat spirometry after 3 months. Safety monitoring was done on all participants during the study.

Results: Participants with COPD, undergoing autologous cellular therapy with PRP-PC, had a statistically significant increase in FEV1% predicted at 3 months post-treatment. In addition, they had a statistically and clinically significant increase in subjective quality of life at 3-, 6-months and 12 months post-treatment. Adverse events were rare and minor and largely related to the process of drawing blood.

Conclusion: Advanced treatments such as autologous cellular therapy with PRP-PC can be a safe, effective option for helping to mitigate the natural progression of COPD. This study and others published in the literature have found significant improvements in pulmonary function

Rubio MM | Volume 2; Issue 2 (2021) | JRMBR-2(2)-015 | Research Article

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.

and quality of life when autologous PRP-PC is used. Current pharmacologic therapies are aimed at relieving symptoms and preventing acute exacerbations, but cellular therapy may alter the progressive decline of chronic lung disease over time. Cellular therapies should be considered as a safe, valuable, potential therapy for these patients. An additional comparative, randomized, double blind study comparing this PRP-PC protocol plus standard of care versus standard of care alone is being planned.

Keywords

Cellular Therapy; Autologous; Platelet Rich Plasma; PRP; COPD; FEV1

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is progressive and life-limiting, with often profound effects on quality of life especially as disease progresses [1]. The median survival time after COPD diagnosis is about 13 years with progressive decline in both lung function and quality of life during that time [2]. Though overall mortality from COPD in the United States has declined somewhat since 2004, there remains an annual mortality rate of 47.8 per 100,000 people or 0.047%, and COPD remains the third leading cause of death [3]. COPD is best described as the chronic limitation of outward airflow arising from a mixture of inflammation, tissue remodelling, and tissue destruction [4,5].

Few new treatments for chronic lung diseases have emerged in recent years. The most common maintenance treatments for COPD include inhaled corticosteroids, beta-2 agonists and anticholinergics. Lung reduction surgery may be considered in patients with emphysema, and lung transplantation may be an option though the availability for donor lungs is scarce. Pharmacologic treatments are aimed at improving symptoms, improving exercise tolerance, and reducing exacerbations, though none have proven to alter the natural course of the disease [4-6].

Mitigating the chronic cycle of lung tissue destruction and reversing, or even curing COPD are ultimate goals. Platelet-based, cellular therapies have begun to address the possibility of altering this cycle and regenerating lung tissue, thereby improving both quantitative lung function measures and subjective quality of life. Platelet-rich plasma, developed from the concentration and activation of platelets from whole blood, can aid in correcting the mediation of inflammation, the immune response and tissue restoration within the lungs [7].

For this study, 419 COPD-diagnosed participants underwent autologous blood-derived Platelet Rich Plasma- Platelet Concentrate (PRP-PC) treatment as an adjunct to their usual pharmacologic care. The primary aim was to evaluate COPD-diagnosed participants' quantitative lung function with baseline and 3-month post-treatment FEV1% predicted values. The secondary aims were to explore changes in participant-reported quality of life at 3, 6 and

Rubio MM | Volume 2; Issue 2 (2021) | JRMBR-2(2)-015 | Research Article

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.

12 months after treatment and to explore and summarize adverse events and mortality data among the cohort. The hypothesis is that cellular therapy, which can enhance a patient's own healing ability within damaged lung tissue, is a safe and effective option for improving quantitative lung function measures and positively affecting quality of life in patients with chronic obstructive disease. Previous studies on PRP-PC therapy in chronic lung disease have shown improvement in both pulmonary function and subjective quality of life following treatment [8,9].

Background

Platelets, anucleate blood cells, are best known for their role in hemostasis, but recent advances in the field of cellular biology have identified a critical link between hemostasis, inflammation, immune modulation, and tissue repair [7]. It was previously thought that COPD patients could benefit from anti-platelet therapy, as mortality risk from cardiovascular events is increased in those with COPD [10].

Research on the beneficial effects of platelet rich plasma therapeutics emerged in 2006 with a description of platelet function in the healing cascade [11]. Since that time, PRP-PC has been investigated in numerous medical applications from bone healing in orthopedics to chronic wound treatment, with the underlying theory that introducing platelet concentrate to an area of injury would stimulate the release of healing bioactive factors [11,12]. During preparation of PRP-PC, multiple bioactive factors are released from the micro particles of activated platelets which are known to recruit adult mesenchymal stem cells, promote angiogenesis, and stimulate endothelial cell turnover. The paracrine mechanism of activated platelets further provides a link between the immune system and tissue repair [13]. In the lungs, the damaged tissue itself may be a chemoattractant for platelet-based bioactive factors, priming the site for regeneration and repair [13]. Because PRP is a living cellular material, its characteristics depend on the characteristics of the source blood, which may change if the patient is in an acute or chronic state [11]. The added advantage of using autologous (patient)-derived PRP-PC is the enhanced safety profile with no known adverse effects, in contrast to pharmaceuticals, lung reduction surgery, and lung transplantation [11].

Platelet concentrates prepared with leukocytes (or the "buffy coat" layer of cells) may additionally regulate CD34 cells to produce a robust anti-inflammatory response [11]. This is especially important in the application of cells for COPD. Leukocytes can affect the intrinsic biology of chronic lung disease. Neutrophils play an important role in host protection against pathogens, angiogenesis, and tissue restoration. B and T-lymphocytes are highly involved in adaptive immunity [11].

Autologous, cellular-based therapy with platelet rich plasma/platelet concentrate derived from and administered through the bloodstream can be a safer and effective treatment for patients with chronic lung disease [11]. These bioactive factors can participate in tissue repair and modulation of the immune system. The most abundant growth factors secreted by activated platelets are Platelet-Derived Growth Factor (PDGF) which promotes collagen synthesis and

Rubio MM | Volume 2; Issue 2 (2021) | JRMBR-2(2)-015 | Research Article

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.

stimulates proliferative activity, Transforming Growth Factor (TGF- β) which enhances collagen synthesis, promotes angiogenesis and promotes chemotaxis of immune cells, Vascular Endothelial Growth Factor (VEGF) which stimulates angiogenesis and the migration of endothelial cells and Fibroblast Growth Factor (FGF) which promotes proliferation of mesenchymal stem cells [14].

Prepared PRP-PC is a pure source of signaling molecules that promote cell proliferation, migration, and differentiation and angiogenesis in their local environment [15]. Preparation of PRP-PC for delivery to the lung tissue for this study was done with the Harvest Terumo SmartPrep[®] branded preparation kit. 60 ml of whole blood was collected from each participant and processed in the on-site laboratory. Activation of growth factors in this manner makes them immediately available to target cells within damaged tissue. In this study, intravenous infusion of the final product was done through the peripheral circulation where the cells travel first to the right heart and then into the pulmonary microcirculation about 15 minutes after harvesting.

Subjects and Methods

All participants were recruited from a cellular therapy clinic based in Dallas, Texas between January 2017 and October 2020. Participants were screened for inclusion prior to treatment. To be included for treatment, all participants were required to have a diagnosis of chronic obstructive lung disease, evidence of unremarkable labs (including a complete blood count and test of kidney and liver function) in the 3 months prior to treatment, a current documented medical history and a current medication list. Participants with a history of cancer within the five years preceding treatment (except for basal cell skin cancer) were excluded. Participants were not to be smoking at the time of treatment, and smoking cessation services were offered by the clinic. All participants reviewed and signed informed consent before treatment. Participants underwent treatment for two consecutive days, each treatment lasting about an hour. A full history and physical examination was performed on each participant on their first day of treatment. Most patients travelled to the clinic from outside of the area. 90% travelled by car and 10% travelled by airplane. Participants were asked to be well-hydrated if not on a fluid restriction and all were encouraged to eat normally prior to treatment.

The average age of participants was 70.9 years. 257 (61.3%) of the cohort were male, 162 (38.7%) female. 375 (89.7%) of the sample were former smokers and 3 (.72%) were current smokers. 245 (58.5%) of the sample required supplemental oxygen at least part of the time.

In-clinic spirometry was performed to assess the forced expiratory volume in 1 second (FEV1) as well as the calculated FEV1% predicted which compares the individual participant against someone of the same demographics without lung disease and what we would predict to be normal for that demographic.

Each participant completed the Clinical COPD Questionnaire (CCQ) on their first day of treatment. The CCQ is a reliable, validated instrument and is endorsed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee for measurement of breathing-

Rubio MM | Volume 2; Issue 2 (2021) | JRMBR-2(2)-015 | Research Article

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.

related quality of life and for response to treatment [16,17]. This scale is a 10-item survey which measures three domains of quality of life related to breathing: symptoms (4 items), mental health status (2 items) and functional health status (4 items). Each item is scored from 0-6 with 0 being "never" and 6 being "all the time". Higher scores indicate poorer quality of life or greater difficulty. The total score is averaged for a final score of 0-6, again with 6 representing poorer quality of life. Total survey scores as well as scale subset scores were analyzed in this study.

Clinically meaningful change is that which is detectable by the participant as either positive or negative. Clinically meaningful change for the CCQ has been defined in the literature as an improvement of 0.4 or more on a 0-6 scale. This is the minimum change needed for participants to feel a meaningful improvement in breathing [18,19].

Spirometry measures and CCQ scores were recorded in the participant's secure medical record and replicated in a secure data repository which was also used for follow-up documentation. 150 participants from the COPD group returned to the clinic after 3 months for follow-up spirometry. All participants were phoned by the research team at 3 months, 6 months, and 12 months after treatment and the CCQ was re-administered and scored. Each of these values were entered into the secure data repository for later analysis. Safety data was collected during and following each treatment for up to one year. This included adverse events as well as mortality data.

Treatment was performed by drawing a sample of whole blood from a vein in the participant's upper extremity via intravenous catheter which remained in place for re-infusion of the final product after preparation. The whole blood was prepared using Harvest Terumo SmartPrepTM commercial, proprietary equipment. Preparation of PRP-PC is complete after approximately 15 minutes and the final cellular product is returned to the patient immediately following preparation.

Results

150 participants returned after 3 months for follow-up spirometry to measure the change in FEV1% predicted after treatment. Their mean age was 71.2 years, approximately 63% male and 37% female, and 93.3% were former smokers. 58% required supplemental oxygen at least part of the time. The most common GOLD stage among participants was stage 4 at 58% of the sample (n=87), followed by stage 3 at 25.3% of the sample (n=38).

Mean pre-treatment, aggregate FEV1% predicted for the group was 32.65% (SD 17.9%) with a range of 11% to 87%. The mean 3 month post-treatment FEV1% predicted improved to 34.3% (SD 18.9%) with a range of 10% to 93%. The resulting change is a mean increase of 1.62% (SD 7.42%) with a range of 43% to 41%. 101 of 150 participants (67.3%) experienced either an improvement or no decline in FEV1% predicted from baseline.

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.

Rubio MM | Volume 2; Issue 2 (2021) | JRMBR-2(2)-015 | Research Article

Each follow-up FEV1% predicted value was calculated against the individual participants' baseline. The average change was an improvement of 7.83% (SD 30.2%) over baseline, with range of 69% decline to an improvement of 241%.

A paired-samples t-test was conducted to examine the aggregate FEV1% predicted difference from baseline to 3 months post-treatment. The test was significantly significant ATP = 0.003.

After aggregate data were examined, each GOLD stage of COPD severity was analyzed separately. We found that those in GOLD stage 2 (n=20) experienced a mean decrease in FEV1% predicted from baseline of 1.53 (SD 21.2%). Participants in GOLD stage 3 (n=38) experienced a mean increase in FEV1% predicted from baseline of 2.62 (SD 11.5%). Those in GOLD stage 4 (n=87) experienced a mean increase in FEV1% predicted from baseline of 12.42% (SD 37.03%).

For quality of life measures, the average total CCQ at baseline was 3.56 (SD 1.05). At 3 months post-treatment, the average total CCQ improved to 2.81 (SD 1.07). At 6 months post-treatment, 2.63 (SD 1.17). And at 12 months post-treatment, 2.82 (SD 1.31). Descriptions of values for each individual domain and tests of statistical significance follow.

Specific to the symptom domain, the baseline average was 3.56 (SD 1.17). At 3 months post-treatment, the average symptom domain score improved to 2.80 (SD 1.21). At 6 months post treatment 2.60 (SD 1.38) and at 12 months post-treatment, 2.78 (SD 1.49). For the mental health domain, the baseline average was 3.83 (SD 1.64). At 3 months post-treatment the average mental health domain score improved to 2.65 (SD 1.77). At 6 months post-treatment 2.26 (SD 1.82). And at 12 months post-treatment, 2.48 (SD 1.72). For the functional health domain, the baseline average was 3.47 (SD 1.32). At 3 months post-treatment the average functional health domain score improved to 2.87 (SD 1.29). At 6 months post treatment, 2.88 (SD 1.45). And at 12 months post-treatment 0.62 (SD 0.43). Each post-treatment time point for all three domains far exceeded the MCID of >/= 0.4 for clinically significant improvement. The mean scores and change scores are represented in Table 1.

Paired-samples t-tests were conducted on each pair of baseline and follow-up scores. The change from baseline to each follow-up interval for both the total CCQ score and individual domains was statistically significant for all domains and at all follow-up intervals. The p-values for each test are represented in Table 2.

Variable	Μ	SD	n	Change	SEM
Symptom Average Baseline	3.56	1.17	419		0.06
Symptom Average 3 Months	2.8	1.21	296	0.76*	0.07
Symptom Average 6 Months	2.6	1.38	212	0.96*	0.09
Symptom Average 12 Months	2.78	1.49	123	0.78*	0.13
Mental Average Baseline	3.83	1.64	419		0.08
Mental Average 3 Months	2.65	1.77	296	1.18*	0.1
Mental Average 6 Months	2.26	1.82	212	1.59*	0.12

Rubio MM | Volume 2; Issue 2 (2021) | JRMBR-2(2)-015 | Research Article

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.

Mental Average 12 Months	2.48	1.72	123	1.35*	0.16	
Functional Average Baseline	3.47	1.32	419		0.06	
Functional Average 3 Months	2.87	1.29	296	0.60*	0.07	
Functional Average 6 Months	2.88	1.45	212	0.59*	0.1	
Functional Average 12 Months	0.62	0.43	123	2.85*	0.04	
'*' indicates the statistic exceeds the MCID of 0.4						

Table 1: Summary Statistics Table CCQ Scores for Participants (n=419).

Variable	Μ	SD	n	p-value
Symptom Average 3 Months	2.8	1.21	296	<.001*
Symptom Average 6 Months	2.6	1.38	212	<.001*
Symptom Average 12 Months	2.78	1.49	123	<.001*
Mental Average 3 Months	2.65	1.77	296	<.001*
Mental Average 6 Months	2.26	1.82	212	<.001*
Mental Average 12 Months	2.48	1.72	123	<.001*
Functional Average 3 Months	2.87	1.29	296	<.001*
Functional Average 6 Months	2.88	1.45	212	<.001*
Functional Average 12 Months	0.62	0.43	123	<.001*
'*' indicates statistical significance at $p < 0$.05			

Table 2: Paired Samples t-tests for Participants (n=419).

In total, 16 adverse events were reported related to treatment (Fig. 1). The most reported of these was lightheadedness following drawing of blood and in all cases responded well to intravenous fluids, juice and/or food. One participant complained of lightheadedness after the blood draw and lost consciousness. That participant responded quickly to intravenous fluids. Emergency response was activated in that case, but the participant did not require additional care. Four participants complained of nausea following the blood draw which resolved prior to discharge.

In one case, the participant's platelets did not separate after centrifugation. It was determined that the participant was on an undisclosed anticoagulation medication that likely prevented adequate separation of his platelets during processing.

In about half of the total number of participants treated for this study, an antioxidant nebulizer treatment, glutathione, was offered and administered if the participant elected to receive it. The action of glutathione is as an antioxidant and mucolytic and was typically accepted by participants who reported coughing and phlegm production. Three participants reported more shortness of breath following administration of glutathione. This was deemed due to the mobilization of phlegm in the airways or bronchoconstriction. The overall incidence of any adverse event for this study was 3.8% (Fig. 2).

Rubio MM | Volume 2; Issue 2 (2021) | JRMBR-2(2)-015 | Research Article

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.

DOI: http://dx.doi.org/10.46889/JRMBR.2021.2201

7

Longitudinal mortality data was obtained on participants in the study. This information was collected either during follow-up phone calls or by the decedents' family calling the clinic to report the death. Not always was the cause of death disclosed or recorded. In total there were 18 patients who died from 2017 to the time of this paper in 2021, an incidence of .043%, which is just slightly lower than the overall annual mortality incidence for COPD in the US as stated in the literature.





Figure 2: Adverse events by type.

Rubio MM | Volume 2; Issue 2 (2021) | JRMBR-2(2)-015 | Research Article

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.

Discussion

Novel treatments for patients with COPD are needed significantly. There has been little progress in prolonging survival for these patients over the years [6].

In this study, we found a statistically significant mean quantitative improvement of 7.83% in FEV1% predicted for GOLD stage 3 and 4 patients just three months after treatment. There was a slight deterioration in FEV1% predicted among those in GOLD stage 2 though this was an extremely small sample size at just 20 participants. It is expected that early intervention is likely to lead to greater beneficial outcomes over time, and therefore we suspect that a larger sample size will be able to demonstrate this.

Measuring subjective change, for patients with COPD at all post-treatment intervals there was both clinically (based on the MCID) and statistically (based on the p-value) significant improvement for all three domains of the CCQ at every post-treatment time point. This remains consistent with previous studies with the same PRP-PC treatment and further support the efficacy of cellular therapy.

The rate of adverse events related to treatment in this cohort was low, minor in nature, and highly related to the drawing of blood rather than treatment itself. The post-treatment mortality of participants in this study was consistent with the general US population and those not treated with PRP-PC.

It is important to note that this study was conducted by means of observation following intervention and was not designed as a clinical trial. This study is therefore limited by the lack of a control group. Ongoing planned research includes a randomized, double-blind, head-to-head comparison of PRP-PC therapy and standard of care with standard of care alone.

Conclusion

Autologous cellular therapy with blood-derived PRP-PC for chronic obstructive lung disease should be considered as an adjunct with the current standard of care to improve patient outcomes. Cellular therapy should also be an option for patients who are unable to tolerate the available standard of care, such as pharmacologic treatment or surgery. The findings of this study, and others in the field, demonstrate overall highly statistically and clinically significant efficacy of autologous, minimally manipulated, and same day administered PRP-PC for chronic lung disease. Although larger-scale and randomized controlled trial studies are being planned, the initial findings of this and other studies show hopeful results for positive outcomes. The safety profile of using adult, autologous cells has been well-documented. Certainly, much more work needs to be done in this arena, but the preliminary results are exciting and are changing the future of medicine.

Rubio MM | Volume 2; Issue 2 (2021) | JRMBR-2(2)-015 | Research Article

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.

References

- 1. Marx G, Nasse M, Stanze H, Boakye SO, Nauck F, Schneider N. Meaning of living with severe chronic obstructive lung disease: a qualitative study. BMJ Open. 2016;6(12).
- Shavelle RM, Paculdo DR, Kush SJ, Mannino DM, Strauss DJ. Life expectancy and years of life lost in chronic obstructive pulmonary disease: Findings from the NHANES III follow-up study. Int J COPD. 2009;4:137.
- 3. Centers for disease control and prevention. COPD: chronic bronchitis and emphysema. [Last accessed on: June 15, 2021] <u>https://www.cdc.gov/nchs/fastats/copd.htm</u>.
- 4. Barnes PJ, Anderson GP, Fagerås M, Belvisi MG. Chronic lung diseases: Prospects for regeneration and repair. Euro Respiratory Rev. 2021;30(159):212-8.
- 5. Lange P, Ahmed E, Lahmar ZM, Martinez FJ, Bourdin A. Natural history and mechanisms of COPD. Respirology. 2021;26(4):298-321.
- Brightling C, Greening N. Airway inflammation in COPD: Progress to precision medicine. Euro Respiratory J. 2019;54(2):1-13.
- 7. O'Sullivan BP, Kerrigan SW. Platelets, inflammation and respiratory disease. The non-thrombotic role of platelets in health and disease. 2015:135.
- Rubio M. Longitudinal assessment of FEV1 change following autologous cellular therapy. J Reg Med Biol Res. 2021;02(01):1-10.
- 9. Coleman J, Rubio M. Regenerative therapy for chronic obstructive pulmonary disease, a retrospective study of benefits and safety. Stem Cell Reg Med. 2018;2(1):1-6.
- Ekström MP, Hermansson AB, Ström KE. Effects of cardiovascular drugs on mortality in severe chronic obstructive pulmonary disease: A time-dependent analysis. American J Respiratory and Critical Care Med. 2013;187(7):715-20.
- 11. Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-rich plasma: New performance understandings and therapeutic considerations in 2020. Int J Molecular Sci. 2020;21(20):1-36.
- 12. Ding Z-Y, Tan Y, Peng Q, Zuo J, Li N. Novel applications of platelet concentrates in tissue regeneration (Review). Experimental and Therapeutic Med. 2021;21(3):1-12.
- 13. Crisci A, Crescenzo U de, Crisci M. Platelet-rich concentrates (L-PRF, PRP) in tissue regeneration: Control of apoptosis and interactions with regenerative cells. J Clin Molecular Med. 2018;1(3):1-2.
- 14. Pavlovic V, Ciric M, Jovanovic V, Stojanovic P. Platelet rich plasma: a short overview of certain bioactive components. Open Med. 2016;11(1):242-7.
- 15. Alves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. Skin Appendage Disorders. 2018;4(1):18-24.
- 16. Van der Molen T, Willemse BW, Schokker S, Ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health and quality of life outcomes. 2003;1(1):1-13.
- 17. Zhou Z, Zhou A, Zhao Y, Chen P. Evaluating the Clinical COPD Questionnaire: A systematic review. Respirol. 2017;22(2):251-62.
- Alma H, De Jong C, Jelusic D, Wittmann M, Schuler M, Flokstra-de Blok B, et al. Health status instruments for patients with COPD in pulmonary rehabilitation: defining a minimal clinically important difference. NPJ Primary Care Respiratory Med. 2016;26(1):1-8.
- 19. Alma HJ, De Jong C, Jelusic D, Wittmann M, Schuler M, Kollen BJ, et al. Assessing health status over time: impact of recall period and anchor question on the minimal clinically important difference of copd health status tools. Health and Quality of Life Outcomes. 2018;16(1):1-3.

Citation: Rubio MM, et al. Platelet Rich Plasma- Platelet Concentrate Therapy in COPD: An Observational Cohort Study. J Reg Med Biol Res. 2021;2(2):1-10.