Original Article

DOI: 10.7860/JCDR/2019/42135.13301

Orthopaedics Section

Early Outcome of Platelet Rich Plasma and Non-steroidal Anti-inflammatory Agent Alone and in Combination on Primary Knee Osteoarthritis

FUNBI AYENI[1], OLUWADARE ESAN[2], INNOCENT CHIEDU IKEM[3], OLAYINKA OLADIRAN ADEGBEHINGBE[4]

ABSTRACT

Introduction: Platelet rich plasma is an emerging treatment modality in managing mild and moderate cases of osteoarthritis. There is no consensus on dose and various combination of this product with other available treatment modalities especially Non-Steroidal Anti-Inflammatory Drugs (NSAID).

Aim: To determine and compare the early treatment outcomes of intra-articular injection of Platelet Rich Plasma (PRP) and oral NSAIDs alone and in combination in mild and moderate knee osteoarthritis.

Materials and Methods: Forty-five subjects with mild and moderate osteoarthritis who met the study criteria were randomly allocated into three intervention groups: Group A: had intra-articular injections of autologous PRP only; Group B: received oral NSAIDs only, while Group C: had both oral NSAID and intra-articular injection of autologous PRP. Subjects in Group A had 3 sessions of injections at monthly interval while Group B had 75 mg of Diclofenac taken daily at 8 am and 8 pm. Subjects in the Group C had both monthly injections of autologous PRP and oral administration of NSAIDs for three months. Outcome measures were severity of pain assessed using Visual Analogue Scale (VAS) and functional outcome using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Data were analysed using the IBM SPSS Statistics Version 22, Armonk, NY; IBM Corp and Comparison of the means were done using analysis of variance (ANOVA).

Results: Better responses in the severity of pain and functional outcome were seen in subjects who had intra-articular administration of autologous platelet rich plasma with or without NSAIDs than in subjects who had only NSAIDs ($p<0.05$).

Conclusion: PRP alone and in combination with NSAID is superior to NSAID only therapy in mild and moderate osteoarthritis.

Keywords: Diclofenac, Intra-articular injection, Non-steroidal anti-inflammatory drugs

INTRODUCTION

Osteoarthritis is a degenerative joint disease afflicting millions of people worldwide [1,2]. The cost of managing this condition is enormous [3-6]. Treatment options that can achieve healing is desirable [7]. Interest in the efficacy of PRP to achieve healing of this condition is increasing due to the presence of growth factor (Platelet derived growth factor) which is able to stimulate healing [8-10]. It is prepared easily and it's autologous in nature, hence limiting the risk of transfusion of infection or reaction. NSAID remains the drug of choice in the management of pain; it offers satisfactory symptomatic relief alongside other modalities of non-operative treatment [11-13]. The drawback of this treatment modality is the undesirable side-effects such as gastric irritation and end organ damage [14]. The question is whether this product alone or its combination with NSAID is better and able to bring about relief of symptom in the short term or not.

The present study was conducted to compare the functional outcome of intra-articular autologous platelet rich plasma and the widely used oral NSAID alone and in combination in patients with mild and moderate knee osteoarthritis.

MATERIALS AND METHODS

It was a prospective study conducted between May 2016 to April 2017 in a tertiary health facility in Southwest Nigeria. Ethical approval was obtained from the Institution's Ethical Committee (IRB/IEC/004553 NATIONAL:NHREC/27/02/2009a) while written consent was obtained from the patients. The study was done in compliance with ethical standard laid down in 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Forty-five consecutive patients who met the inclusion criteria were recruited into the study. These are the patient with mild/moderate knee osteoarthritis who were willing to receive either of the treatments. Patients with rheumatoid arthritis, post traumatic osteoarthritis, pregnancy, thrombocytopenia were excluded from the study.

Detailed patient assessment was carried out including the clinical history, examination, full blood count, plain radiograph of the knee. Patients were categorised into mild/moderate osteoarthritis using the Kellgreen Lawrence grading [15] and outcome measures of the treatment were evaluated using WOMAC and VAS [16,17]. Scoring was done by the same individual.

Consecutive patients were serially recruited into 3 Groups (A,B,C). Group A had only intra articular PRP while Group B had oral NSAID and Group C had a combination of oral NSAID (Diclofenac preparation) and intra articular PRP.

PRP was prepared from 20 mL of whole blood obtained from the ante-cubital vein using a sterile bottle preloaded with citrate phosphate dextrose-adenine. This was initially centrifuged at 1,800 RPM for 15 minutes following which the supernatant was obtained and further subjected to centrifugation at 2,500 RPM for a further 15 minutes to separate the plasma and platelet. The PRP obtained were randomly subjected to platelet count using auto analyser to be sure the correct concentration of platelet was present. Three millilitres of suspended platelet rich plasma were administered into the joint using standard landmark. This procedure was repeated at 4 weekly intervals for maximum of 3 doses. Patients in Group C had in addition to the injection, oral administration of diclofenac up to the end of the intervention phase of the study. Patients randomised into Group B had only oral diclofenac (arthrotec75 mg 12 hourly) which was administered as necessary, but not more than twice in a day.

Potential confounders such as therapy that can influence the study (pain) were disallowed as patients that required further medication or therapy were excluded from the study. Subjects were followed-up on monthly basis for 6 months with routine evaluation of the patient using WOMAC questionnaire and VAS score.

STATISTICAL ANALYSIS

Data were analysed using the IBM SPSS Statistics Version 22. Armonk, NY; IBM Corp. Data were expressed as mean unless otherwise indicated. Mean and standard deviation of the WOMAC, VAS was calculated. Comparison of the means was done using analysis of variance (ANOVA).

RESULTS

Forty-five patients were recruited into three groups. The mean age of the population was 60.2±11.7 years with a range of 41 years to 85 years. Sixty percent of the subjects had bilateral involvement of the knee while the rest had unilateral involvement [Table/Fig-1].

Gender	Female 16 (35.6%) Male 29 (64.4%)
Mean age	60.2±11.7 years
Mean BMI	28.1±6.0 kg/m^2
Laterality	Bilateral 27 (60%)
	Unilateral 18 (40%)
Employment	Retiree 20 (44.4%)
	Trader 16 (35.6%)
	Teacher 2 (4.5%)
	Civil servant 7 (15.5%)

[Table/Fig-1]: Showing the socio-demographic distribution of the population.

All the three groups experienced an improvement in a similar trend with the commencement of the treatment. At the commencement of the study, all the groups had similar mean VAS score (p=0.630) but at the end of this study, the mean VAS were 1.46 and 1.66, respectively in Group A and C while Group B had 4.26 and this was statistically significant (p=0.001)

Significant differences in the VAS score were found in the 5th month, as the groups that had only NSAID was found to have a statistically significant VAS than groups who had a form of intra-articular administration of PRP [Table/Fig-2].

Time of observation	Mean of visual analogue scale score			df	F	p-value
	Group A	Group B	Group C			
1st month (pre-treatment)	5.46	5.06	5.86	2	0.46	0.63
2nd month	3.40	2.53	3.40	2	1.08	0.35
3rd month	2.26	2.13	1.80	2	0.44	0.65
4th month	1.73	1.93	1.80	2	0.11	0.89
5th month	1.46$^{\alpha,c}$	3.73$^{\beta}$	1.66$^{\alpha,c}$	2	11.27	0.001*
6th month	1.46$^{\alpha,c}$	4.26$^{\beta}$	1.66$^{\alpha,c}$	2	13.07	0.001*

[Table/Fig-2]: Analysis of variance of the mean of visual analogue scale score of the intervention groups.
VAS: Visual analogue scale; *: statistically significant difference p≤0.05; α: Group differs significantly from type (in row) when β is indicated; c: Group does not differ significantly from type (in row)

There was an initial improvement in symptoms up to the 4th month after which there was a significant difference in the mean WOMAC score of the group of patient who had only NSAID (Group B) and those who had any form of PRP administration.

At the 6th month, the mean WOMAC score were 13.40 and 22.23, respectively in the Group A and C while Group B was 44.0 which was found to be significantly greater than the other groups (p=0.001) [Table/Fig-3].

Time of observation	Mean of the WOMAC Score			df	F	p-value
	Group A	Group B	Group C			
1st Month (Pre-Treatment)	41.85	46.40	49.98	2	0.32	0.73
2nd Month	27.97	23.61	29.59	2	0.60	0.56
3rd Month	21.06	21.74	25.28	2	0.29	0.75
4th Month	15.42	19.15	22.30	2	1.03	0.37
5th Month	13.35$^{\alpha,c}$	40.54$^{\beta}$	22.10$^{\alpha,c}$	2	13.45	0.001*
6th Month	13.40$^{\alpha,c}$	44.00$^{\beta}$	22.23$^{\alpha,c}$	2	15.94	0.001*

[Table/Fig-3]: Analysis of variance of the mean of the WOMAC score in the intervention groups.
*: statistically significant difference p≤0.05; α: Group differs significantly from type (in row) when β is indicated; c: Group is not statistically different from type (in row)

DISCUSSION

Early outcome measures (VAS and WOMAC) of this study revealed that intra-articular platelet rich plasma administration in the knee joint has the capacity to improve the symptoms experienced by patient with mild and moderate knee osteoarthritis immediately and up to 3 months after the last administration.

However, the result obtained in Group A (PRP only) cannot only be explained by the chondrogenesis theory which is expected to take effect much later. It is likely that the effects of PRP in the knee joint is beyond chondrogenesis as revealed by early resolution of pain and improved activity level in this study. Investigators have proposed that PRP is likely to have a whole lot of wider impact on the joint beyond chondrogenesis proposing that other effects could be due to reduction of synovial membrane hyperplasia, cytokine modulation which may be responsible for the early effects while other factors will be responsible for the pain controlling effect subsequently [9,18,19].

The present authors found that all patients experienced an improvement in their symptoms within the 1st month of receiving PRP injection in the present series. Patel S et al., also found the mean duration of benefit after the 1st injection was 17.63 days [18]. This further lay credence to the fact that chondral remodelling which would have started later and lasted longer could not solely explain the effects of PRP.

The improvement in the VAS and WOMAC observed within the first three months of platelet rich plasma intra-articular could suggest that it may have an immediate action on the joint which is comparable in efficacy with the NSAIDs but with the advantage of an extended action lasting up to the 6th month of the study.

The present study found that patients in PRP group had significant alleviation of their symptoms compared to those in NSAID. A similar outcome was found in a similar study that compared PRP with Acetaminophen where subjects revealed a significantly better outcome in the PRP group for up to 6 months [20]. The combination of platelet rich plasma and NSAIDs as a form of therapy in the management of osteoarthritis have not been extensively studied and it has been postulated that the anti-inflammatory actions of NSAIDs may impair the inflammatory stage of cartilage repair that is meant to be an effect of the platelet rich plasma. This may be the reason why we found a better response both to pain and function in PRP group only compared to Group C subjects (PRP combined with NSAID) though this was not statistically significant. It is also believed that PRP has inhibitory effect on joint inflammation by acting against NF-kβ pathway [21]. Hence combination of both is expected to be synergistic which we did not find in the present study.

LIMITATION

The authors acknowledge the fact that the present study was limited to mild/moderate cases of osteoarthritis as authors only

recruited Grades 1 and 2 using the Kellgren-Lawrence system. The follow-up period was short therefore a study that will consider the above limitation will help in further shedding light to this treatment modality.

CONCLUSION

In conclusion, the present authors found early efficacy following intra-articular platelet rich plasma administration in the treatment of mild and moderate knee plasma regardless of its combination with NSAID. It should be offered as one of the first line of treatment in indicated patients giving its immediate effect on the patients' symptoms.

REFERENCES

[1] Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nature Reviews Rheumatology. 2019;6:625-35.
[2] Ogunlade SO, Oginni LM, Nwadiaro HC, Popoola O, Eweani UN, Onabowale BO, et al. The efficacy and toleration of celecoxib (Celebrex) in the treatment of osteoarthritis in Nigeria: a multicentre study. West Afr J Med. 2005;24:263-67.
[3] Centers for Disease Control and Prevention (CDC). Prevalence and most common causes of disability among adults--United States, 2005. MMWR Morb Mortal Wkly Rep. 2009;58(16):421-26.
[4] Lawrence RC, Hochberg MC, Kelsey JL, McDuffie FC, MedsgerJr TA, Felts WR, et al. Estimates of the prevalence of selected arthritic and musculoskeletal diseases in the United States. J Rheumatol. 1989;16:427-41.
[5] Arya R, Jain V. Osteoarthritis of the knee joint: An overview. Journal, Indian Academy of Clinical Medicine. 2013;14:154-62.
[6] Raeissadat SA, Rayegani SM, Babaee M, Ghorbani E. The effect of platelet-rich plasma on pain, function, and quality of life of patients with knee osteoarthritis. Pain Res Treat. 2013,7:165967. https://www.hindawi.com/journals/ Assessed on 14th January 2018
[7] Gobbi A, Karnatzikos G, Mahajan V, Malchira S. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis preliminary results in a group of active patients. Sports Health: A Multidisciplinary Approach. 2012;4:162-72.
[8] Rabago D, Best TM, Zgierska AE, Ziesig E, Ryan M, Crane D. A systematic review of four injection therapies for lateral epicondylosis: prolotherapy, polidocanol, whole blood and platelet-rich plasma. British Journal of Sports Medicine. 2009;43:471-81.
[9] Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini M, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid visco supplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2011;27:1490-501.
[10] Mishra A, Woodall J, Vieira A. Treatment of tendon and muscle using platelet-rich plasma. Clinics in Sports Medicine. 2009;28:113-25.
[11] Jordan KM, Arden NK, Doherty M, Gunther K, Hauselmann H, Herro-Beaumont G, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Annals of the Rheumatic Diseases. 2003;62:1145-55.
[12] Doherty M. The efficacy of Arthrotec® in the treatment of osteoarthritis. Scandinavian Journal of Rheumatology. 1992;21:15-21.
[13] Gan TJ. Diclofenac: an update on its mechanism of action and safety profile. Current Medical Research and Opinion. 2010;26:1715-31.
[14] Gamble R, Wyeth-Ayerst J, Johnson EL, Searle WA, Beecham S. Recommendations for the medical management of osteoarthritis of the hip and knee. Arthritis & Rheumatism. 2000;43:1905-15.
[15] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16:494-02.
[16] Bellamy N. Validation study of WOMAC: a health status instrument for measuring clinically- important patient-relevant outcomes following total hip or knee arthroplasty in osteoarthritis. J Orthop Rheumatol. 1988;1:95-108.
[17] Burckhardt CS, Jones KD. Adult measures of pain. The McGill Pain Questionnaire (MPQ), Rheumatoid Arthritis Pain Scale (RAPS), Short Form McGill Pain Questionnaire (SF-MPQ), Verbal Description Scale (VDS), Visual Analogue Scale (VAS), West Haven-Yale Multidisciplinary Pain Inventory (WHYMPI). Arthritis Rheum. 2003;49:S96-104.
[18] Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. The American Journal of Sports Medicine. 2013;41:356-64.
[19] Wu W, Chen F, Liu Y, Ma Q, Mao T. Autologous injectable tissue-engineered cartilage by using platelet-rich plasma: experimental study in a rabbit model. Journal of Oral and Maxillofacial Surgery. 2007;65:1951-57.
[20] Simental-Mendía M, Vílchez-Cavazos J, Peña-Martínez V, Said-Fernández S, Lara-Arias J, Martínez-Rodríguez H. Leukocytepoor platelet-rich plasma is more effective than the conventional therapy with acetaminophen for the treatment of early knee osteoarthritis. Arch Orthop Trauma Surg. 2016;136:1723-32. https://doi.org/10.1007/s00402-016-2545-2.
[21] Yin W, Xu H, Sheng J, An Z, Guo S, Xie X, et al. Advantages of pure platelet-rich plasma compared with leukocyte- and platelet rich plasma in treating rabbit knee osteoarthritis. Med Sci Monit. 2016;22:1280–90. https://doi.org/10.12659/MSM.898218.

PARTICULARS OF CONTRIBUTORS:
1. Department of Orthopaedic Surgery and Traumatology, Obafemi Awolowo University/Teaching Hospitals Complex, Ile-Ife, Osun, Nigeria.
2. Department of Orthopaedic Surgery and Traumatology, Obafemi Awolowo University/Teaching Hospitals Complex, Ilelfe, Osun, Nigeria.
3. Department of Orthopaedic Surgery and Traumatology, Obafemi Awolowo University/Teaching Hospitals Complex, Ilelfe, Osun, Nigeria.
4. Department of Orthopaedic Surgery and Traumatology, Obafemi Awolowo University/Teaching Hospitals Complex, Ile-Ife, Osun, Nigeria.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Oluwadare Esan,
Department of Orthopaedic Traumatology, Faculty of Clinical Sciences,
Ile-Ife, Osun, Nigeria.
E-mail: seunkayo@yahoo.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 31, 2019
- Manual Googling: Jul 31, 2019
- iThenticate Software: Oct 28, 2019 (7%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: No
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **May 30, 2019**
Date of Peer Review: **Jul 05, 2019**
Date of Acceptance: **Aug 03, 2019**
Date of Publishing: **Nov 01, 2019**