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Research Article

Effect of Addition of Hyaluronic Acid on Platelet Rich Plasma in Treatment of Chronic Osteoarthritis

Rabi'u MB[1*] and Aliyu DA[2]

[1]Department of Anaesthesia: Abubakar Tafawa Balewa Teaching Hospital Bauchi, Nigeria
[2]Department of Laboratory Sciences, Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria

*Corresponding Author
Rabi'u MB

Abstract: **Background**: Osteoarthritis, one of the common musculoskeletal diseases, affects about half of the world population at some point in their lives. It is associated with pain and functional limitations. The use of autologous platelet rich plasma (aPRP) either alone or in combination with hyaluronic acid (HA) for treatment of knee osteoarthritis will continue to get attention due to its anti-inflammatory and growth factors releasing effects, viscous-supplementation effect of hyaluronic acid and the side effects of the commonly used NSAIDs.The aim of this study was to compare the effectiveness of addition of hyaluronic acid to platelet rich plasma in the treatment of chronic osteoarthritis knee-joint..**Methods:** Following the approval of our institutional Ethical Review Committee, fifty two patients who had non-traumatic chronic osteoarthritis of knee joint pain (>3 months) and kellgren-lawrence score of 2 and 3, were randomized into two groups, A and B. Group A had intra-articular injection of 4 mls autologous PRP, 300 IU of HA and with 2 mls of 0.5% plain bupivacaine and Group B received intra –articular injection of 4 mls autologous PRP plus 2 mls of 0.5% plain bupivacaine administered blindly. Pain intensity and functional disability were assessed, with numerical pain rating (NPR) scale and pain disability questionnaire (PDQ), at 1, 3 and 6 months follow up. **Results:** Majority of the patients (90.4%) were in the age range of 41-60 years. What is the M: F ratio? At 6 months follow up, significant reductions in pain intensity (NRS) in the two groups were observed 7.15 ±1.0 vs 1.33±0.5 and 7.10 ± 1.2 vs 2.65±1 respectively for groups A and B. The lower pain score observed among group A at 6 months follow up was statistically significant, $p<0.05$. There was an improvement in functional activity (assessed by activity rating scale) among both groups. Pre intervention, 25.9% and 74.1% of patients in group A had moderate and severe limitations to movement respectively in comparison with 70.4% who reported no limitation and 29.6% with mild limitation to movement at the end of 6 months follow up. Similarly, 22.0% and 78% of patients in group B had moderate and severe limitations to movement respectively before treatment. At the end of 6 months follow up, 56% and 42% of patients in group B had no limitation and mild limitation to movement respectively. There is lower PDQ scores among Group A patients, indicating better functional and psychological improvement. **Conclusions**: The study revealed that addition of Hyaluronic acid to autologous platelet rich plasma provides significant pain reduction, improvement in psychological and functional capacity compared with platelet rich plasma alone in patients with chronic osteoarthritis of knee joints**.**

Keywords: Osteoarthritis of knee joint, autologous platelet rich plasma and hyaluronic acid.

INTRODUCTION:

Osteoarthritis (OA) is one of most common musculoskeletal disease, is a chronic degenerative joint disease characterized by progressive destruction of articular cartilage, narrowing of joint space and crepitus over the join and results in thinning and eventual wearing of articular cartilage thus resulting in painful, limited joint movement which impair daily functional activity (Raeissadat, S.A. *et al*., 2015; Kon, E. *et al*., 2011). The degeneration of articular cartilage is mainly due to changes in the activity of chondrocytes, which also involves other joint tissues, as alterations of the meniscus, sclerosis and edema in the underlying subchondral bone as well as intermittent inflammation of synovium (Raeissadat, S.A. *et al*., 2015; Kon, E. *et al*., 2011; Ishijima, M. *et al*., 2014; Chen, W.H. *et al*., 2014). Osteoarthritis (OA) may affect almost half the

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population at some point in their lives through pain and decreased functional capacity (Russo, F. *et al*., 2016).

The use of autologous platelet-rich plasma (APRP) to treat osteoarthritis (OA) is increasing, although the long-term effects of PRP remain controversial (Kon, E. *et al*., 2011). The high concentration of autologous growth factors in PRP is expected to reduce the time needed for healing based on the current clinical and research evidences (Lio, K. *et al*., 2009). Therefore, use of platelet rich plasma for treatment of Knee joint OA will continue to get attentions due to improvement in quality of life from reduction in pain and improvement of functional activity from the growth factors released from APRP (Lio, K. *et al*., 2009; Pietrzak, W.S., & Eppley, B.L. 2005).

Hyaluronic acid (HA) is widely used to treat OA of the knee joint (Ishijima, M. *et al*., 2014), the beneficial effects of HA are attributed to its function as a viscosupplement and its anti-inflammatory activity. Several reports that compare the clinical outcomes achieved with HA and PRP for OA have been published (Lio, K. *et al*., 2009; Pietrzak, W.S., & Eppley, B.L. 2005; Chen, W.H. *et al*., 2014). However, the clinical results of simultaneous HA and PRP injections has not been well studied especially in Africa and Sub-sahara region were the economic burden of the disease and the cost of surgery is high. Chen *et al*., (2014) published an in vitro study of the synergistic actions of HA when combine with PRP on cartilage regeneration in OA. In that report, the combination of HA and PRP reduced the levels of pro inflammatory cytokines and increased articular chondrocyte proliferation and chondrogenic differentiation. The authors concluded that the observed synergistic effects were the result of different molecular mechanisms. Hyaluronic Acid (HA) intra-articular injections are widely accepted for the treatment of pain associated to OA. The goal of HA viscosupplementation is to reduce pain and improve viscoelasticity of synovial fluid. Autologous platelet-rich plasma (APRP) has been used to treat OA to possibly induce cartilage regeneration. The combination of HA and APRP could provide many advantages for tissue repair. Indeed, it compliment HA viscosupplementation with APRP regenerative properties (Russo, F. *et al*., 2016; Lio, K. *et al*., 2009). Combining APRP and HA may benefit from their dissimilar biological mechanisms and help in improving pain and functional capacity of the patients with knee joint osteoarthritis and also provide information about the impact of this rare approach in improving quality of life, among large populations of patients suffering from this common disease condition. (Russo, F. *et al*., 2016; Lio, K. *et al*., 2009; Pietrzak, W.S., & Eppley, B.L. 2005).

The aim of this study is to determine the effectiveness of single injection of autologous platelet rich plasma as monotherapy for treatment of mild-moderate knee joint osteoarthritis compared with combination of autologous Platelet rich plasma and Hyaluronic acid.

MATERIALS AND METHOD

This is a prospective randomize single blind study of 56 patients with moderate osteoarthritis stage 2 and 3 based on the Kellgren-Lawrence classification between March 2015 and febuary 2017 attending private pain clinic . The standing position anterior-posterior and lateral radiographic films of all patients were evaluated. Staging was made based on the Kellgren-Lawrence classification. Patients with bilateral knee joint osteoarthritis, diabetes mellitus, metabolic syndrome, coagulation disorders, and Kellgren-Lowrence class 4 and four patients 2 from each group that lost to follow up were excluded from the study.

Patients were randomised using sealed enveloped into Group A those that had intra-articular PRP and HA administered and group B those that had only PRP intra-articular injection. Tweenty six patients (26 knees) were involved in the PRP and HA group and 26 patients (26knees) were involved in the PRP only group. Prior to the procedure all patients had clinical evaluation including routine full blood count to ascertain adequacy of platelet count and an inform consent was obtained. Demographic variables, base line Numerical rating score, Pain disability scale and activity related scale was used to assesed limitation to range of movement were recorded. Platelet rich plasma was prepared from 15 mL of autologous venous blood taken from the upper extremities. The blood was put into a 15 mL centrifuge tube containing 1.5 mL 3.2% sodium citrate and centrifuged at room temperature for five minutes at 3,600 rpm. After the centrifuge, 4 ml of PRP was obtained between the bottom erythrocyte and upper plasma layers using just above the buffy coat.

The knee joints were prepared using povidone Iodine and a sterile cover, 2 ml of 1% plain lidocaine was used for infiltration of the intended procedure site to provide anaesthesia at the injection site. The procedure were done via the anterolateral portal using size 25G needle. After 5 minutes of injection, patient activity related pain was assessed and reduction of pre intervention pain activity related by 50-75 % was consider as diagnostic for successful intra articular injection. Patients were observed for one hour and were sent home accompanied by responsible adults and advised to take one day of rest and apply ice to the area. After the first day, the patients were permitted to carry out tolerable daily activities. Doluxetine 30 mg was recommended as a pain reliever. The patients in both groups were evaluated using pain disability questionnaire before intervention and at one and six months follow up respectively and numerical rating scoring was also assessed pre intervention and at one months and 6 months follow up respectively.

RESULTS

Table 1: Demographic variables

Variables	Groups	
	Group A	**Group B**
Age years	54.35±15.12	57.35±6.67
Sex M/F	4/22	5/21
Weight Kg	76.62±12.62	65.96±11.61
Height M2	1.56±0.3	1.55±0.4
Duration months	21.23±9.79	19.85+10.24

Table 1: showed the mean age of the study population was 54± 5.12 and 57.35±6.67, male to female ratio was1:5 and 1:4 for group A and B respectively. Group A patients had longer duration of onset of joint pain 21.23±9.79 compared to group B 19.85±10.24.

Table 2: Numerical rating scores and pain disability scores

Variables	Pre -intervention	Post -Intervention	
		1month	**6 months**
Group A Numerical Rating score	7.15±10.78	3.73±7.11	2.08±0.89
Pain disability score			
Psychological	29.23±8.32	20.16±3.34	17.62±2.90
Functional	68.84±13.94	48.80±5.20	37.38±8.08
Group A			
Numerical Rating score	7.12±0.65	4.50±1.03	2.8±0.74
Pain disability score			
Psychological	31.84±10.78	26.12±3.21	21.80±7.0
Functional	68.78±9.54	54.21±8.47	44.88±10.2

Table 2: showed reduction in numerical rating pain from 7.15±10.78 to 3.73±7.11 at one month and further reduction to 2.08±0.89 at 6 months follow up. Functional and psychological score on pain disability scale were significantly decreased at 6 months follow up.

Table 3 Joint involved and Radiological grading (Kellgren-Lawrence classification)

Variables	Groups	
	Group A (n=26)	**Group B (n=26)**
Joint involved		
Right	17 (65.4%)	21(80.8%)
Left	9 (34.6%)	5(19.2%)
Grade		
Grade II	19(73.1%)	15 (57.7%)
Grade III	7 (26.9%)	11(42.3%)

Table 3: showed right knee joint was affected in about 65.4% and 80.8% of the patients in group A and B respectively. However majority 73.1% of the patients in group A have radiological grade II affectation compared to 57.7% among group B patients.

Table 4: Activity related scale

Variables	Pre-intervention	Post- intervention	
		1month	**6months**
Group A (n=26) No limitation of movement	-	-	4(15.4%)
Mild limitation of movement	-	9(34.6%)	18 (69.2%)
Moderate limitation of movement	7 (26.9%)	17 (65.4%)	4 (15.4%)
Severe limitation of movement	19 (73.1%)	-	-
Group B (n=26)			
No limitation of movement	-	-	-
Mild limitation of movement	-	2(7.7%)	1(3.8%)
Moderate limitation of movement	10(38.5%)	23(88.5%)	17 (65.4%)
Severe limitation of movement	16(61.5%)	1 (3.8%)	8 (37.3%)

Table 4: showed improvement in activity related score among the study groups

Table5: Pair T-test table Pre and 6 months Post Intervention

Variables	95% CI Lower	Upper	T-test value	*P*-value
Group A: Pre and Post Intervention PDS				
NRS	5.05	6.11	39.52	< 0.001
Functional	26.05	36.86	11.99	< 0.001
Psychological	8.56	15.36	7.25	< 0.001
Group B: Pre and Post Intervention PDS				
NRS	4.15	4.77	29.91	< 0.001
Functional	17.20	28.87	8.13	< 0.001
Psychological	6.75	13.01	6.50	< 0.001

CI: Confidence Interval, PDS: Pain Disability Score, NRS: Numerical Rating Score

DISCUSSION

Our study showed preponderance of osteoarthritis among female gender, with right knee joint most affected. This study revealed significant reduction of base line pain score among patients that received addition of hyaluronic acid (HA) in autologous platelet rich plasma (aPRP) compared to patients with intra articular injection of autologous platelet rich Plasma alone p<0.001 this indicated better clinical improvement in patients that received intra-articular injection of hyaluronic acid and platelet rich plasma than platelet rich plasma only. The Significant reduction in pain score was found at 6 months after the injection, this is due to the facts that the stimulatory effect is seen mainly after months, these findings suggested that stimulatory effect of HA on growth factor release seems to appear slowly (Lio, K. *et al*., 2009; Pietrzak, W.S., & Eppley, B.L. 2005).The finding of this study is similar to the study conducted by K. Lio *et al*., (2009), the authors reported that aPRP can stimulate the healing process of different tissues by delivering various growth factors and cytokines that are released by platelets. The authors concluded that adding HA to the aPRP would increase the concentration of growth factors released with resultant decrease in pain compared to when platelet rich plasma is used alone. Similarly, other studies reported both HA and aPRP have potential to enhance the cartilage healing process and slow down the progression of Osteoarthritis (OA) therefore, may provide better clinical improvement than either is used alone (Pietrzak, W.S., & Eppley, B.L. 2005; Weiser, L. *et al*., 1999; Kon, E. *et al*., 2011), these findings suggested that, there may be a potential additive effect and significant improvement in clinical features when aPRP is combined with HA in treating OA, however, there is limited studies in literature that examined the combination use of HA and aPRP.

Activity related scale was used to assessed joint mobility among the patients, both groups had certain limitation to range of movement from moderate limitation 38.5% and 26.9% to severe limitation 61.5% and 73.1% for group A and B respectively, our study found better improvement in range of movement among the patients that received hyaluronic acid plus platelet rich plasma with significant improvement at 6 months follow up compared to those that received platelet rich plasma alone. Several Studies showed that HA provides appropriate matrix and supportive scaffold material for cartilage repair and enhances the mechanical properties of the cartilage (Spaková, T. *et al*., 2012). Thus, it is hypothesized that their combination may be synergistic. According to available data, combining aPRP and HA may benefit from their dissimilar biological mechanisms and helped in with anti-inflammatory properties, catabolic enzymes, cytokines and growth factors (Russo, F. *et al*., 2016). Also, it was demonstrated that the association of HA plus aPRP showed synergic effects in the potentials regenerative and anti-inflammatory in comparison to aPRP alone (Kon, E. *et al*., 2011; Andia, I., & Abate, M. 2014). This association can alter the inflammatory cytokines in the degeneration process of the chondrocytes through specific mediators (CD44, TGF-βRII) and also promote the regeneration of cartilage and inhibit inflammation in osteoarthritis (OA). The time to all these modifications happen is between 1 to 3 months after application, which explains the reason for delayed significant improvement in activity related movement up to six months seen in our study (Chen, W.H. *et al*., 2014; Zhu,Y). Both functional and psychological pain disability score on pain disability scale were reduced in both study group, however reduction of the scores was found to be higher among the patients that received intra articular injection of hyaluronic acid and Platelet rich plasma, indicating better quality of life among the group, this may be due to the benefit from their synergistic and dissimilar biological mechanisms (Russo, F. *et al*., 2016; Lio, K. *et al*., 2009; Pietrzak, W.S., & Eppley, B.L. 2005; Zhu,Y). Although our findings revealed intra-articular injection of aPRP has shown pain remission, functional and psychological improvement, but not majority of patients had clinical improvement at 6 months when compared to patients that received Combination of aPRP and HA. Kellgren-Lawrence classification is a radiological classification of knee joint osteoarthritis used in our study and is graded 1 to 4, the severity of the disease increases the higher the scores. In our study majority 73.1% of the patients that received addition of hyaluronic acid in platelet rich plasma had radiological grade II compared to 57.7% among those that received platelet rich plasma alone, this may resulted in better clinical outcome observed among the former group. However, similar findings was reported by Zhu Y *et al*., that Combining HA and aPRP resulted in significant pain reduction and less functional limitation compared to HA alone up to 1 year after treatment.

CONCLUSION

This study revealed that, addition of HA to autologous aPRP provides significant pain reduction, improvement in psychological and functional capacity compared with platelet rich plasma alone in patients with chronic osteoarthritis of knee joints. More randomized controlled studies with larger numbers of patients and longer duration of follow up are needed to confirm long term beneficial effects observed.

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