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ORIGINAL ARTICLE

Platelets Rich Plasma versus Its Combination with Hyaluronic Acid in Knee Osteoarthritic Pain Management.

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ABSTRACT

Background: Osteoarthritis is a degenerative painful disease of joints that is commonly affected knee joints. multiple modalities were used in management as medical treatment, steroid injections but with limited effect, Platelet-rich plasma therapy is a new era in treatment modality that stimulates the natural healing process ,as it contain multiple growth factors and had many advantages. Aim of the work is to compare the effectiveness and duration of combining Platelet-rich plasma with hyaluronic acid versus Platelet-rich plasma alone in relieving pain with knee osteoarthritis.

Methods: After approval of our ethical committee and written informed consent from patient, this clinical trial study was done in Zagazig university hospital, anesthesiology department, pain clinic unit in the period from January 2018 to January2020. This study included 100 patients ASA (American society of anesthesiologist) grade I&II into two groups; I (n=50) patients injected by intra-articular platelet rich plasma and hyaluronic acid(HA), II (n=50) patients injected by intra-articular PRP only. patients were evaluated using the Knee Society Scoring System and the visual Analog scoring system before treatment and at one , three , six, twelve and eighteen months after treatment.

Results: There was a significant difference between both groups regarding visual Analog scoring system at 6th, 12th and18th months ($P < 0.0001$) more in group I, also there was a significant difference between both groups regarding Knee Society Scoring at 12 and 18 month ($P < .027$ and $P < 0.014$ respectively) more in group I. Also there was a significant improvement of visual Analog scoring system and Knee Society Scoring in both groups after treatment with P value < 0.0001.

Conclusion: Intra-articular Platelets rich plasma plus hyaluronic acid was more durable and efficient than the platelets rich plasma alone in management of knee osteoarthritis.

Keywords: Platelets rich plasma, Knee osteoarthritis, Intra-articular injection and Hyaluronic acid

INTRODUCTION

Osteoarthritis (OA) is a progressive painful joint disease associated with cartilage degeneration, It is common with advanced age in knee joint causing knee osteoarthritis (KOA) that disturbs their daily activities [1,2]. To improve movement and relieve pain of OA, multiple nonsurgical therapeutic modalities ranging from oral chondroprotectives, non-steroidal anti-inflammatory (NSAID), intra-articular steroids and vesico supplements had been tried. Platelet-rich plasma (PRP) is a promising solution for various conditions like musculoskeletal injuries and joint arthritis [3]. Intra-articular PRP is a new therapeutic modality in management of KOA as it is easily prepared from patient's blood which is then centrifuged by special technique to obtain PRP that contain Platelet alpha-granules which release numerous growth factors, as platelet-derived growth factor, hepatocyte growth factor , vascular endothelial growth factor and transforming growth factor-b [4] all of them decreases catabolism of chondrocytes and improves its secretory function, stimulates collagen II and prostaglandin synthesis and thorough increase joint homeostasis and help chondral remodeling [3-5][3,5,6] PRP stimulate chondrocyte proliferation ,new vascular and cellular growth that helps tissue regeneration [7][8] accelerates the physiological healing process at the injected site, relieves pain and shows anti-inflammatory and anti- bacterial activity [9,10]

.although all this advantages it had minimal effect in treating patient with late stages of OA, only anti-inflammatory effect by regulation of joint homeostasis [9,11].

Stimulated Synoviocytes increase physiological hyaluronic acid secretion. PRP decreases interleukin-1 (IL-1) and increases matrix metalloproteinases (MMPs) and so decreases matrix degeneration [2, 11, 12].

Some studies suggested that complex interaction of PRP within joint might positively influence chondrocyte apoptosis and contains insulin like growth factor that inhibits chondrocytes degeneration. [13, 14].

HA is a natural component of the connective tissue and cartilage. It is the viscoelastic component of the synovial fluid, it also functions as a physiological nutrient factor , with increase the body weight the amount of intraarticular lubricant decreased and so patients are liable to OA on long-term so HA can be injected intra-articularly in patients with OA [15-17].

METHODS

After approval of our ethical committee and written informed consent from patient , this clinical trial was done in Zagazig university hospital, anesthesiology department, pain clinic unit in the period from January 2018 to January 2020. This prospective comparative study included 100 patients ASA American society of anesthesiologist) grade I&II suffering from pain due to KOA grade 3 according to the Kellgren-Lawrence(KL) classification The KL classification was described using anteroposterior view knee radiographs. Which was assigned a grade from 0 to 4, with its correlation to increasing severity of K OA, with Grade 0 signifying no presence of OA and Grade 4 signifying severe K OA. Additionally, KL provided detailed radiographic descriptions of KOA [18]. The Kellgren and Lawrence classification system have been used in research the original description: Grade 0 (none): definite absence of x-ray changes of osteoarthritis

Grade 1 (doubtful): doubtful joint space narrowing and possible osteophytic lipping

Grade 2 (minimal): definite osteophytes and possible joint space narrowing

Grade 3 (moderate): moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends

Grade 4 (severe): large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends [19-21]

All patients were subjected to full clinical and laboratory examination. patient with diabetes mellitus, other rheumatic diseases, coagulation disorders, infection, immunosuppressive diseases ,patients receiving anticoagulants or non-steroidal anti-inflammatory drugs within five days prior to the intervention and patient with KOA stages 4 were excluded from the study.

Patients were divided into two groups; (group I n= 50) patients (3 males &47 females) received 5ml of PRP intra-articular for three sessions two weeks apart followed by intra-articular hyaluronic acid 90 mg once . (Group II n= 50) patients (6 males &44females) received 5ml of PRP intra-articular for three sessions two weeks apart. Patients were reevaluated regarding KSS and VAS at 1st day, 1st month, 3rd, 6th, 12th, 18th months.

Preparation of PRP: 40–50 cc of venous blood were obtained in sterile sodium citrated tubes using an 18G needle this for preparation of 5 cc PRP with platelet concentration of 4–6 times the average normal value, the anticoagulated blood was centrifuged twice: first for 10 at 1000 rpm minutes to separate erythrocytes; second centrifugation at 4000 rpm for 5 minutes to concentrate platelets. The final product was 4-5 cc of PRP free leukocytes. Calcium chloride was used for PRP activation (0.01- 0.04 mL of 10% calcium chloride /1 mL of PRP. calcium chloride was injected after intra-articular PRP injection). Technique: Patient lies in supine position with slight knee flexion and supported, determine the injection site commonly the inferiomedial or inferiolateral side to patella injection was done under guidance of ultrasound machine (US) using high frequency US probe. After treatment patient should not have any (NSAID) and any knee pain or inflammation was managed by oral paracetamol and cold foment .the procedure was repeated three times two weeks apart ,patients were evaluated every one month for eighteen months by using KSS and VAS (0 -3=no pain, 4-6 = mild pain , ≥ 7 sever pain) [22][23][24] but we reported VAS score and KSS at three ,six , twelve and eighteen month . the Knee Society Clinical Rating System (KSS) was designed to provide a simple and objective scoring system to rate the knee and patient's functional abilities before and after total knee intervention it assisted the following point : pain, Total Range of Flexion ,Alignment (Varus & Valgus) Stability (Maximum movement in any position) Walking Walking aids used stairs The original KSS has a "Knee Functional Score .it is scored from 0 to 100 with lower scores being indicative of worse knee conditions and higher scores being indicative of better knee conditions [25][26].

Grading for the knee Society Score

Score	Excellent	Good	Fair	Poor
80-100	Score 70-79	Score 60-69	Score below 60	

Sample size:

Assuming the mean KSS score among PRP group vs HA group was 75.75+_13 vs 68.26+_13.7.At

80% power and 95% CI, the estimated sample will be 100 cases, 50 cases in each group Open epi.

STATISTICAL ANALYSIS

Data were statistically analyzed using SPSS 20 for Windows (SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± SD. Categorical variables were analyzed using the $\chi 2$ test and continuous variables were analyzed using the student's t-test. P<0.05 was considered statistically significant.

RESULTS

There was a significant difference between both groups regarding visual Analog scoring system at 6th, 12th and18th months (P < 0.0001) more in group I, also there was a significant difference between both groups regarding Knee Society Scoring at 12 and 18 month (P <.027 and P< 0.014 respectively) more in group I. Also there was a significant improvement of visual Analog scoring system and Knee Society Scoring in both groups after treatment with P value < 0.0001.

Table (1): Demographic data of patients in both groups

	Group I n=50	Group II n=50	P.value
Sex	Male 3 Female 47	Male 6 Female 44	
Age	58.8±6.2 year	59.8 ±7.1year	0.43
Stage: 3	(50)	(50)	
BMI (Kg/m²)	30.1±3,3	31.3 ±4.9	0.15

Data was expressed as mean ± SD
P value: ≥ 0.05 not sig.

Table (2): Comparing KSS score between both groups: Pre-treatment, 1st, 3rd, 6th, 12 and 18 months after treatment.

	Group I n=(50)	Group II n=(50)	P.value
Pretreatment	58. 4± 6.7	59.2±6.3	0.54
1st month aftertreatment	63.2±7.6	62.1±8.1	0.484
3rd month aftertreatment	72±5.3	72.2 ± 3.	0.81
6th	89±4.6	88.6±1.2	0.56
12th After treatment	89±4.1	88.3±1.9	0.027*
18th After treatment	90±1.6	88±2.1	0.014*

Data was expressed as mean ± SD
P value: ≥ 0.05 not sig.,*= p ≤ 0.05 sig. , **=p ≤ 0.001 highly sig
KSS:Knee Society Scoring System

Table (3): Comparing VAS score between both groups: Pre-treatment, 1st, 3rd, 6th, 12 and 18 months after treatment.

	Group I n=(50)	Group II n=(50)	P value
Pretreatment	7.3± 1.1	7.1±0.9	0.322
1st month aftertreatment	4.3±0.8	4.2±0.6	0.48
3rd aftertreatment	3.3±0.1	3.4±0.3	0.08
6th aftertreatment	2.1±0.3	2.8.±0.1	0.0001*

	Group I n=(50)	Group II n=(50)	P value
12th aftertreatment	3 .5±0.3	4.±0.8	0.0001*
18t aftertreatment h	3.1	4±1.1	0.0001*

Data was expressed as mean ± SD
**=Pvalue :0.001≤ highly sig.
VAS score visual analogues scale score

DISCUSSION

Platelets rich plasma (PRP) is an autologous blood product that has highly concentrated platelets; it is an evolution in pain medicine and phototherapy therapy, for treating musculoskeletal and joints pain **[15, 16]**.Our results show that there were no statistically significant differences between the studied groups as regards patient's age, sex, body mass index BMI and grade of osteoarthritis. also no significant difference between pretreatment period and at 1 rst , 3rd and 6th month after intra articular injections between the studied groups as regard KSS but there was significant difference regarding KSS between GI and GII at 12th (89±4.1) (88.3±1.9) and18 months(90±1.6)(88±2.1) this could be explained due to the effect of PRP as it contain higher amounts of collagen II and prostaglandin (PG) act as anti-inflammatory and enhance chondrocyte function in joints remodeling and this in agree with Park et al and Pereira et al they found that PRP decreases catabolism of chondrocytes and improves its function as it stimulates collagen II and prostaglandin synthesis causing remodeling of joints **[3, 5]**. and the effect of HA in increasing joint lubrication **[15]**.PRP injections were found to produce statistically significant improvements in overall KSS and VAS scores for patients with knee osteoarthritis up to 12 months after intervention Dold etal **[23]**.in contrast to our result PRP might not have a direct effect on the chondrocyte anabolic process in late stage OA, but an anti-inflammatory effect through the regulation of joint homeostasis and cytokines level **[9, 11]**.Sanchez et al and Zhang et al. , reported a new technique for injection of PRP when used as intraosseous infiltration of PRP combined with intra-articular injection to treat severe KOA they reported good out come after PRP injections. And this in agree with our result although their study include higher number of patient and the patient represented by advanced stage of KOA **[27- 29]**.
Our study showed the efficacy of intra-articular injections of both groups in patients with knee OA, as clinical improvement in pain score VAS score up to 6 month but there was significant difference in group I over group II till 18 month and when comparing pretreatment and post treatment in the same group there is significant improve pain score and functional of joints without complications. And this in agree with Lana et al, they divided patient into three groups (HA plus PRP in group versus PRP alone in group versus HA alone in group in patient with mild to moderate knee OA they noticed better outcomes regarding duration and function in patients who treated with both (HA plus PRP) over HA alone up to one year and over PRP alone up to three months **[29, 30]**. Anitua et al. found that PRP with HA had synergistic action, by enhancing chondrocyte action and it is better than PRP alone [30].Both HA and PRP are biological approaches and their use are critical in the initial phase of OA joints to improve healing ,this in agree with Dallari et al. **[31]** regarding improve function and quality of life (pain, movement flexion and extension , climbing stairs,..) which expressed as KSS our results showed there was no significant difference between both groups until 12th month but there was significant difference in group I over group II froo12th month till 18 month that combination of (PRP plus HA) in group I was more efficient in improving pain ,movement ,climbing stairs and so quality of life this in agree with Calis et al, found that when inject PRP three times at 2weeks intervals to patients with grade 3 and 4knee OA reported improvements in their quality of life, and causes reduction pain score **[12].**
Chang et al found that patients receiving PRP had better and prolonged improvement than those receiving HA **[32]** also Laudy etal found that PRP injections reduced pain and improved function more effectively than placebo or HA injections in patients with KOA **[33]**.

CONCLUSION

Platelet rich plasma therapy is a simple, easy and minimally invasive intervention which is injected in osteoarthritic knee joint to treat degenerative lesions of knee. Its combination with hyaluronic acid is ideal combination as it gives prolonged duration with excellent pain relieve and KSS improves.

Conflict of Interest: None.

Financial Disclosures: None.

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