RESEARCH ARTICLE

CORRELATION BETWEEN RISK FACTORS AND CLINICAL OUTCOMES FOLLOWING INTRAARTICULAR INJECTION OF AUTOLOGOUS PLATELET RICH PLASMA IN EARLY OSTEOARTHRITIS KNEE

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Manuscript Info

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Abstract

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Introduction: Osteoarthritis (OA) knee is one of the major cause of disability particularly in the elderly .Management of OA knee with intraarticular Platelet Rich Plasma (PRP) is an emerging new technique.

Aim : Aim of our study was to assess the efficacy of intra-articular injection of platelet rich plasma (PRP) in knee osteoarthritis and to investigate the correlation between risk factors likeBody mass index ,ageandseverity of osteoarthritis with clinical outcome after intraarticular injection of platelet rich plasma

Study setting : Department of Physical Medicine and Rehabilitation,Government Kilpauk medical college, Chennai, India, from March 2021 to January 2022.

Materials and methods : 64 patients with mean age of 56.52 ±7.53 who were diagnosed with grade 1 and 2 knee OA and who had undergone 2 doses of intraarticular injection of PRP were selected for the study and we retrospectively analysed the role of age, BMI, and Kellgren Lawrence grade of OA knee and their correlation with clinical outcome after intervention .Outcome measures used wereVAS and WOMAC scores

Results: VAS and WOMAC scores before the procedure and final outcome after procedure using wilcoxn signed rank test showed that there was significant improvement in the outcome scores measured at followup done at 4th month . Subgroup analysis of patients stratified for age, Body mass index (BMI) and, KLgradewas performed for determining the individual effect of each risk factor on the outcome scores . It is found that the effect of PRP on people with BMI less than 25 ,KL grade 1 and age group <60 ,is significantly better than subjects with BMI more than 25 ,KL grade 2 and age group > 60 years.

Conclusion: The use of intraarticular platelet-rich plasma definitely improves functional outcome in patients with OA and results in improved quality of life. Higher KL and risk factors like increased age, and BMI, has shown poorer outcome when compared to younger subjects , with lower BMI and KL grade , and hence modification in treatment protocol can be considered for such patients.

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Introduction:-

Osteoarthritis is a progressive degenerative disorder of multifarious aetiology affecting joints. Degeneration of articular cartilage, subchondral sclerosis ,hypertrophy of osseous margins, and morphological changes of synovial membrane and joint capsule are characteristically found in osteoarthritis .It is one of the most common rheumatic diseases affecting elderly and knee joint is the most commonly involved joint with increasing prevalence with age and body mass index.[1] Knee OA is an important public health issue and is one of the major causes of disability.

After numerous researches, it is presently acknowledged that osteoarthritis is a dynamic and complex process, involving plethora of multiple factors including inflammatory, mechanical, and metabolic factors that results in failure of the articular surface to serve its role of absorbing and dispersing the mechanical burden through knee joint that at last prompts cartilage degeneration and further morphological alterations in the joint .[2,3]

Conservative methods like physical modalities, weight reduction ,exercise therapy including strengthening exercises though can control osteoarthritis ,commonly fail due to poor adherence to the treatment. Many of the disease modifying OA drugs (DMOADS) are yet to prove their efficacy.

Recently, use of intraarticularorthobiologic injections for the treatment of OA knee has increased and correspondingly number of research studies evaluating the efficacy of Orthobiologics , platelet rich plasma being the most commonly used , has also increased.

Platelet rich plasma which is a platelet concentrate is rich in growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor, insulin-like growth factor (IGF 1), β-Transforming growth factor, cytokines and are found to help in chondrogenesis. Most of the systematic reviews and meta-analysis on use of use of platelet rich plasma show promising results.

After literature search we understood that association of risk factors and clinical outcomes after PRP injections were not analysed much . We intended to do this study to determine the short term(4 months) efficacy of PRP injections in Kellgren–Lawrence grade 1 and 2 osteoarthritis knee and to evaluate whether there is any correlation between the risk factors like BMI, age and grade of OA knee with clinical outcomes after the treatment.

Materials and Methods:-

Ethical approval for the present study was requested and obtained from the institutional ethics committee (protocol id: 473/2021).

Study Area and period :
Department of Physical Medicine and Rehabilitation,Government Kilpauk medical college, Chennai, India, from March 2021 to January 2022

Study Population:
Patients who diagnosed with knee OA as per ACR criteria and who underwent intraarticular injection of PRP who fulfilled criteria as described below.

Inclusion Criteria:
1. Age:>40 years
2. Symptoms > 3 months
3. KL grade I and II osteoarthritis knee(Kellgren- Lawrence grading),
4. Knee pain unresponsive to conservative treatment for 3months,
5. Stiffness:<30mts

Exclusion Criteria:
1. KL grade 3 and 4 of osteo arthritis knee
2. Polyarticular diseases
3. Steroid treatment in the last 3 months,
4. Ligament or meniscal injury ,

5. Trauma,
6. Cellulitis ,
7. Rheumatoid arthritis

Study design:
Retrospective study

Baseline investigations like Complete blood count ,ESR,CRP were also done. Anthropometric measurements were recorded. Visual analogue scale and WOMAC score were recorded before the procedure , after 1 month,2months and 4 months for all patients undergoing interventional procedures as per our department protocol . 2 doses of intra-articular PRP injection were given for each patient one month apart   . We retrospectively reviewed patients who completed followups . 64 patients were selected from the population for the study and they were assessed and divided into groups based on BMI, KL grade and age .

Fig 1:- Knee radiograph showing Grade 2 OA Knee.

Fig 2:- Ultrasound guided intraarticular injection of platelet rich plasma.

Outcome measures :
Visual Analogue Score :
The visual analogue scale (VAS) is a validated, subjective measure for acute and chronic pain, Scores are recorded by making a handwritten mark on a 10-mm line that represents a continuum between "no pain" and "worst pain. .Using a ruler, the score is determined by measuring the distance between the "no pain" anchor and the patient's mark. Higher score indicates greater intensity of pain

WOMAC Index
Western Ontario and McMasterUniversities Arthritis Index is a pain index measurement for OA, which is widely used for assessing knee joint function .It is a tool for evaluating disorders related to OA of the lower extremities . It consists of a total of 24 questions and three subscales. Among them, there are five questions related to pain, two questions related to stiffness, and 17 questions related to difficulties in doing activities of daily living in relation to physical function. The disease- specific tool is used to assess clinical evaluation of changes in pain-related health status and functional outcomes

Procedure of PRP preparation:
32 ml of whole blood is collected from the subject after Informed consent is obtained.

Whole blood is collected in tubes in which Acid Citrate Dextrose was added(ratio 6:1)

From our previous department study we had developed a protocol for customised autologous platelet rich plasma preparation to obtain PRP with maximum platelet count .[4]

We are following double spin method with RCF of 100 g and 400 g respectively for first and second spin for a duration of 10 minutes each to obtain 4-5ml of leukocyte poor platelet rich plasma. Centrifuge used is 8 holed bucket type table top REMI centrifuge.

4ml of autologous PRP mixed with 0.4ml calcium gluconate was injected intraarticularly by superolateral approach under ultrasound guidance to affected knee joint.

Subjects were observed for any adverse reactions, for 60 minutes after the procedure, and were asked to report immediately if increased pain, swelling or hypersensitivity reactions develops .All analgesics including NSAIDS, were discontinued at the beginning of the study and only paracetamol/ acetaminophen was prescribed for pain control. The procedure was repeated after 4 weeks . VAS and WOMAC were recorded during all follow ups .

Statistical Data Analysis:
Data entry and analysis-
The data were entered using Microsoft Excel 2019 software package and the data sheet was imported into SPSS version 26 for data analysis. Per-protocol analysis was done

Descriptive statistics –
The basic statistics, frequency for qualitative variables and mean and standard deviation for quantitative variables were obtained for baseline characteristics.
Categorical variables were expressed as the absolute number of cases and percentage.Normal distribution of the parameters was checked using Shapiro-Wilk test. For continuous variables, differences between means were calculated with the T-test and for those variables not normally distributed, Mann Whitney U test was used. Independent t test was used in case of normally distributed variables or else non parametric Wilcoxon signed rank test was used to compare continuous matched pre operative and final data. Categorical variables were calculated using he Chi-square or Fisher's exact test. For comparison of means, ANOVA was used in case of continuous normally distributed variables or Kruskal-Wallis test was used as a non parametric test in two or more independent comparison groups. Repeated measures ANOVA was used to compare quantitative variables with multiple follow up measures.

Pearsons' Correlation was used to correlate bivariately between continuous or ordinalvariables which are distributed normally. Correlation was significant at the 0.05 level and0.01 (2-tailed) . The significance threshold for tests was set at $p < 0.05$.

Results:-

Total number of patients who underwent 2 doses of intraarticular PRP injections and completed followup within the study period of 11 months were 64. The role of BMI , KL grade, age,were analyzed with univariate and multivariate analysis to identify the correlation of these risk factors with the outcome after intervention .

Demographic data and characteristics of patients at baseline evaluation were analysed .

Table 1 demonstrates the mean, standard deviation and range values of demographic data and the characteristics of patients at baseline evaluation. Among 64 patients enrolled in the study, mean age of the patients was found to be 56.52 ±7.53. The age ranges between 43 and 70. The mean BMI was 24.75 ± 2.73 and the BMI value ranges between 20.4 to 29. The study group consists of 23.4% males and 76.6% females. Among them, majority 46.9% were right sided OA knee. The imaging data showed that majority of them (71.9%) were graded as KL grade 2. The functional scores depicted that the mean values of VAS and WOMAC scores were decreasing from pre treatment data to final data while the standard deviation values are increasing. This explains that the treatment has significant effect on the study population.

Table 1:- Demographic data and characteristics of patients at baseline evaluation.

DEMOGRAPHIC DATA	Mean Value	Standard deviation	Range
Number of patients	64	-	-
Age, yr	56.52	7.53	43 to 70
BMI	24.75	2.73	20.40 to 29.00
Male/female	15(23.4%)/49(76.6%)	-	-
Diagnosis (side)			
Left	16(25%)	-	-
Right	30 (46.9%)	-	-
Left, bilateral	6(9.4%)	-	-
Right , bilateral	12 (18.8%)	-	-
IMAGING DATA:			
KL Grade 1	18 (28.1%)	-	-
KL Grade 2	46 (71.9%)	-	-
FUNCTIONAL SCORES:			
VAS 0	7.29	0.76	6.0-8.5
VAS 1	5.71	1.09	3.0-8.0
VAS 2	4.41	1.37	1.0-7.0
VAS 4	2.68	1.48	1.0-7.0
WOMAC 0	61.13	7.47	44-76
WOMAC 1	45.11	7.09	30-66
WOMAC 2	36.37	7.85	14-56
WOMAC 4	24.27	9.57	10-56

KL – Kellgren Lawrence grading ; VAS – Visual Analogue Scale , WOMAC –Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2 shows significant results while comparing the results of pre test and final test of VAS and WOMAC using wilcoxn signed rank test. Overall there was significant improvement of outcome scores measured at followup done at 4th month .

Table 2:- overall results of outcome measures and differences from baseline to final follow up.

	Pre	Final	Mean difference	95% CI	p Value
VAS	7.29 ± 0.76 (Range : 6.0-8.5)	2.68 ±1.48 (Range : 1.0-7.0)	-0.19	-0.76-0.37	<0.005*
WOMAC	61.13 ±7.47 (Range : 44-76)	24.27 ± 9.57 (Range : 10-56)	36.86	34.46-39.25	<0.005*

*significant p value (wilcoxon signed rank test)

Subgroup analysis of patients stratified for age, BMI and, KL grade as performed for determining the individual effect of each risk factor on the outcome scores .

The stratified results of VAS and WOMAC based on BMI , age and KL grade during final followup of patients who underwent PRP injection were analyzed.(table 3 and 4) . It is found that the effect of PRP on people with BMI less than 25 is significantly better than people with BMI more than 25 with respect to WOMAC(p value- 0.04) score and VAS(p value -0.003) score . The effect of PRP on people with KL grade 1   and age group <60 ,is significantly better than people with KL grade 2 and age group > 60 years with respect to VAS (p value – 0.032 and and 0.026 respectively)and WOMAC(p value – 0.002 and 0.004 respectively) scores.

Table 3:- The stratified results of VAS during final followup in patients who underwent PRP injections.

	VAS		P value
BMI	**<25 (n=31)** 1.82 ±0.80 (range: 1 to 3)	**>25 (n=33)** 3.49 ± 1.52 (range: 1 to 7)	0.003*
AGE	**<60 (n=42)** 2.57 ± 1.58 (range 1 to 7)	**>60 (n=22)** 2.89 ± 1.27 (Range:1 to 6)	0.026*
KL GRADE	**1 (n=18)** 2.11 ± 0.96 (range: 1to 3)	**2 (n=46)** 2.90 ±1.59 (range: 1 to 7)	0.032*

Table 4:- The stratified results of WOMAC during final followup in patients who underwent PRP injections.

	WOMAC		P value
BMI	**<25 (n=31)** 19.06 ±5.95 (range: 10 to 31)	**>25 (n=33)** 29.15 ± 9.81 (range: 12 to 56)	0.04*
AGE	**<60 (n=42)** 22.60 ± 9.67 (range: 10 to 56)	**>60 (n=22)** 27.45 ± 8.73 (Range:14 to 43)	0.004*
KL GRADE	**1 (n=18)** 21.67 ± 7.57 (range: 11 to 31)	**2 (n=46)** 25.28 ± 10.14 (range: 10 to 56)	0.002*

* significant p values.

Sample size of age groups and KL grade were unequal in stratified results whereas that of BMI was comparable . Estimated marginal means of WOMAC score compared with BMI at various time intervals shows the peaking of the graph as increases more than 25 .(graph 1) .

Graph 1:- Estimated marginal means of WOMAC score compared with BMI at various time intervals.
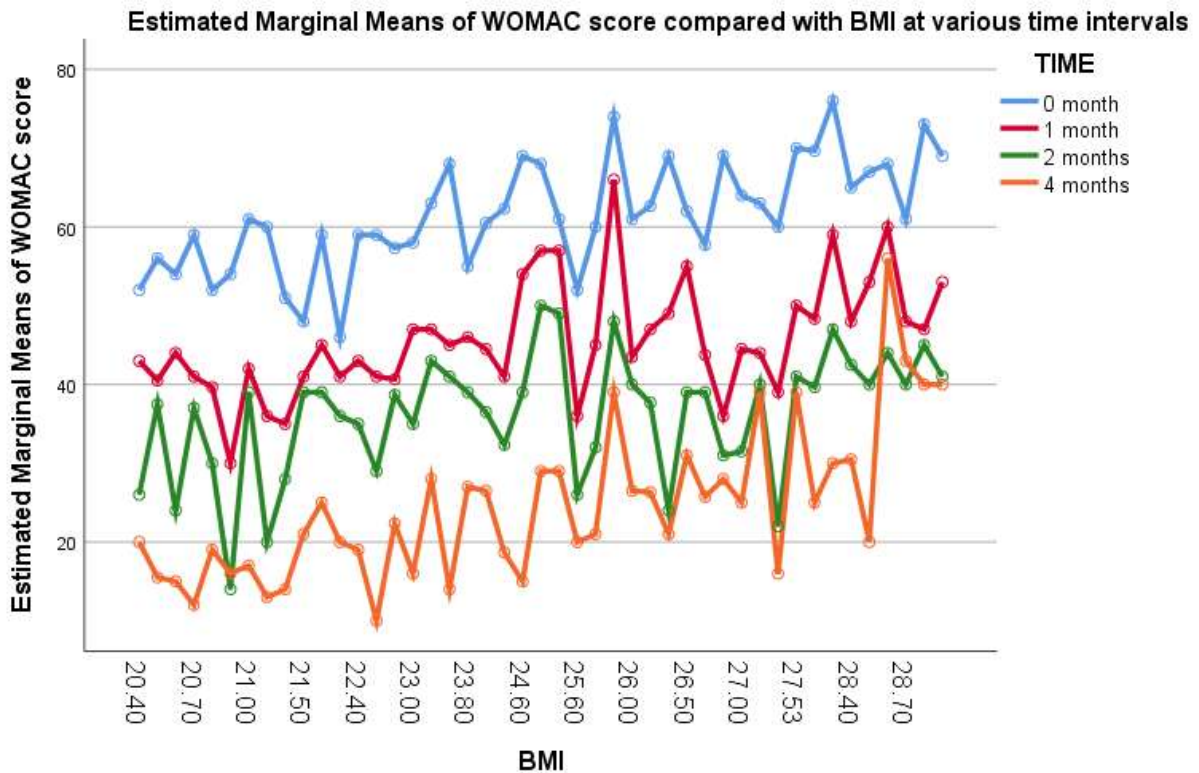
Discussion:-

Primary objective of our study was to evaluate the short term efficacy of PRP injections in OA knee . 2 doses of intraarticular injection of PRP has significantly improved symptoms and functional outcome in our study population. Patel et al in his study compared single dose of PRP injection with 2 doses of PRP injection 3 weeks apart and placebo . On analysis he found out that single dose of leukocyte poor platelet rich plasma was as effective as two doses of platelet rich plasma in improving functional score in terms of WOMAC index,. Both the groups had a better outcome when compared to placebo .[8]

Secondary objective of our study was to assess the correlation of risk factors like KL grade , age, BMI with clinical outcomes after intraarticular PRP injection . These risk factor correlation can help us in anticipating the poor outcome and modifying our mode of treatment .

Old age has already been identified as an important risk factor for OA knee . The minimum age of the population was 43 years and maximum age was 70 years [10]. The increasing occurrence of OA with age can be due to any variety of risk factors and biologic changes that leads to reduced synovial fluid ,decreased viscosity of synovial fluid,cartilage degeneration, sarcopenia causing muscle weakness,reduced bone mineral density, oxidative stress.

Previous studies prove that BMI and stage of OA is positively associated with knee osteoarthritis in men and women [10,11] . MattiaAlessio-Mazzola1,et al in their study of risk factor predictive for failure of OA knee treatment, reported that BMI and high KL grade have significant role , predictive for failure .[9] Certain other studies showed inconsistent association . Filardo et al reported a better outcome in younger subjects with lower degree of cartilage degeneration, which is similar to our study .[13]

PRP has shown effectiveness in early osteoarthritis in most of the studies . A consensus on PRP describes PRP as efficient treatment for early OA knee . They also recommend PRP for severe OA Knee with relative agreement.[7] Yoshitomo et al reported that effectiveness of PRP injections depends on the severity of knee osteoarthritis ; in a study about predictors of effectiveness of PRP.In this study no association was found between age and the effectiveness of PRP therapy [6]

Association of BMI with OA knee has been a research topic of interest . Our study showed that there is definite correlation between BMI and functional outcome even after 2 doses of PRP injections .Few patients who had shown improvement in VAS and WOMAC score after 2 months had a recurrence of pain and decline in functional activities after 4 months . Literature search also brings out similar results. In a study with small sample size , done by Filardo G et al,,they found that BMI significantly influence the clinical outcome in OA knee treated with leukocyte poor PRP , similar to our study. [12]

Considering the efficacy of PRP for the treatment of OA knee , since the older age group , and people with increased BMI and higher grade of OA has shown poorer outcome after 2 doses of PRP , multiple doses can be given in such people for better outcome.

Conclusion:-
The use of intraarticular platelet-rich plasma definitely improves functional outcome in patients with osteoarthritis with symptoms such as pain, joint stiffness and results in improved quality of life. Our study shows that risk factors like increased age and BMI, and higher KL grade has shown poorer outcome when compared to younger subjects , with lower BMI and KL grade . Weight reduction and earlier intervention with intraarticular platelet rich plasma are expected to bring about better outcome .

Limitations:
This study has a few limitations . Sample size was low for a substudy analysis and it was a retrospective study . Only short term efficacy and correlation with risk factors were assessed in this study .Only clinical outcome scores were analyzed.

Future scope and recommendations :
We propose future studies with larger sample size,and longer follow up period for analysing long term effects of PRP in correlation to risk factors .

Multiple doses of PRP can be considered for a better outcome in people withrisk factors like increased BMI and older age group and people with higher grade of OA knee .

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