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RESEARCH ARTICLE

COMPARISON OF CONVENTIONAL DISEASE MODIFYING ANTI-RHEUMATIC DRUGS WITH AND WITHOUT INTRA-ARTICULAR PLATELET RICH PLASMA INJECTION IN THE ALTERATION OF DISEASE PROGRESSION OF EARLY RHEUMATOID ARTHRITIS: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background and Objectives: Rheumatoid arthritis (RA) is a symmetric inflammatory polyarticular arthritis, where autoimmune response causes chronic inflammation and destruction of joints leading to deformities and affecting the activities of daily living. ACR recommends early diagnosis and aggressive treatment of RA with combination disease modifying anti-rheumatic drugs (DMARDs). Although it attenuates disease progression, long-term remissions have not been adequately achieved. Injection of platelet rich plasma(PRP) decrease joint inflammation by modulating synovial cell proliferation, differentiation and inhibition of catabolic pathways.

Aim:to compare conventional DMARDs with and without intra-articular platelet rich plasma injection in wrist joint in the alteration of disease progression of early rheumatoid arthritis.

Methods:A randomized controlled trial, done among newly diagnosed patients of Rheumatoid Arthritis affecting wrist joint, in Department of PMR, RIMS. Data collected in pretested structured proforma and analysis for Pain, Disease activity, USG grading and hand function done using Chi-square test, student's t-test, repeated measure ANOVA test.

Results: There is significant improvement in VAS, DAS28, Cochin scale and USG Grade in study group at the end of 8 weeks, however at 20 weeks it is found to be comparable and p-value is not significant.

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Conclusion: Addition of Intra articular PRP in wrist along with DMARDs has early and better improvement in pain and delay disease progression. Intra-articular PRP injection under USG guidance helps in reduction of synovial inflammation and pain, improvement in function and a safe treatment modality. Early treatment and reduction of disease activity by intervention in targeted joint may delay joint deformity and disability.

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Introduction:-

RA is a symmetric inflammatory polyarticular arthritis that mainly affects the small joints of hands and feet[1]. It has a complex pathogenesis that involves cells of innate and acquired immune systems, activated B and T cells are directed at self-antigen revealing an underlying autoimmunisation process by forming autoantibodies like Rheumatoid Factor (RF) and Anti Citrullinated Protein Antibody (ACPA)[2].

When RA is left uncontrolled, patient may experience joint deterioration, severe disability, decreased quality of life, onset of comorbidities and premature mortalities[3].

According to musculoskeletal ultrasound scoring system (US10) developed by Luz et al[4].Synovial blood flow can be evaluated by power doppler ultrasound (PD) and graded on a semi quantitative score.

Grade 0: No flow in synovium
Grade 1: Single vessel signals
Grade 2: Confluent vessel signals in less than half the area of the synovium
Grade 3: Vessel signals in more than half the area of the synovium

The 2015 ACR guideline for the treatment of RA defined Early Rheumatoid arthritis as RA with duration of disease/symptoms of 6 months. ACR recommends early diagnosis and aggressive treatment of RA with combination DMARDs[5,6].Although it attenuates disease progression, long-term remissions have not been adequately achieved. Keeping in view the shortcomings, newer modalities for management are currently emerging. PRP injection in the affected joint is one of them.

Therapeutic PRP concentration contains about 3-8 times the normal circulating levels (~1 million/ml). Intra-articular injection of PRP decrease joint inflammation by modulating synovial cell proliferation, differentiation and inhibition of catabolic pathways[7].

Our objective was to compare conventional DMARDs with and without intra-articular platelet rich plasma injection in wrist joint in the alteration of disease progression of early rheumatoid arthritis.

Material and Methods:-

A randomized controlled trial done in Department of Physical Medicine and Rehabilitation(PMR), Regional Institute of Medical Sciences(RIMS), Imphal for period of two years. Patients presenting with pain and morning stiffness around the wrist joint attending OPD during the study period were included in the study.

Inclusion criteria:

1. Patient fulfilling 2015 American College of Rheumatology criteria for adult early RA
2. Grey scale ultrasound finding of joint effusion and synovial hypertrophy without bone erosion
3. Age group : 18-50 years

Exclusion criteria:

1. Patient with wrist deformity
2. Thrombocytopenia
3. Anticoagulation medications
4. Acute and chronic infections

Sample size was calculated using the formula $N = (Z\alpha + Z\beta)^2 (S_1^2 + S_2^2)/(m_1 - m_2)^2$. Taking into consideration the study conducted by Mortada et al[8] in 2017a sample of 23 was calculated and considering a dropout rate of 10%, 25 patients were taken in each group giving a total sample size of 50 patients. Patients who met inclusion and exclusion criteria were recruited based on availability and willingness to take part in the study until sample size of 50 was reached. Randomization was done using block of four technique and patients were allocated into two groups namely A=intervention group and B=control group. A list of 12 blocks was prepared to reached a sample size of 48, 49th and 50th was allocated A and B by simple random allocation. For each selected blocks, there was sequence of treatment options. The sequence of treatment option in each block was put in an envelope and sealed. Corresponding envelope was labelled 1, 2, 3, 4....upto 50 according to the appearance of treatment allocation in each selected block. The sealed envelope with label 1 was opened only when we had the first eligible patient and the treatment was allocated.

Control group received standard treatment i.e. triple combination DMARDs therapy (Methotrexate 10mg once weekly + Sulphasalazine 500mg twice daily + Hydroxychlroroquine 300mg once daily) whereas in Intervention group ultrasound guided intra-articular PRP injection was given in the wrist joint along with oral triple combination DMARDs therapy. Single blinding was done where assessors are blinded [Fig 1,2].
Study variables were

Independent variables:
1. Age in completed years
2. Gender
3. Duration of symptoms
4. Intervention
A. Intra-articular injection of Platelet rich plasma + Triple combination DMARDs therapy
B. Triple combination DMARDs therapy

Dependent variables:
1. Pain measured by using Visual Analogue Scale (VAS)

The visual analogue scale is a validated scale for subjective measure of pain. It consists of a 10 cm horizontal or vertical line with the endpoints defining extreme limits such as 'no pain at all' and 'pain as bad as it could be'. Patients were asked to mark their pain level that they feel on the line between the two endpoints which represents the perception of their current state. The distance along the line in cm from the 'no pain at all' end of the VAS to the patient's mark represents the numerical index of the severity of pain.

2. Disease activity using Disease Activity Score 28 (DAS 28-ESR)

The DAS 28 is a system developed and validated by the EULAR to measure the progress and improvement of RA. The number of tender and swollen joints were counted out of 28 joints comprising of shoulder, elbow, wrist, all 5 metacarpophalangeal joints and proximal interphalangeal joints and knee in both side. In addition, the erythrocyte sedimentation rate was measured and the patient made subjective assessment of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible". DAS28 values range from 2.0 to 10.0 while higher values mean a higher disease activity.

3. Disease progression by Power doppler ultrasound study [Fig 2,3]

Power doppler ultrasound was used to evaluate the intra-articular signals due to synovial blood flow and graded on a semi quantitative score (PDSQ)
Grade 0: no flow in synovium
Grade 1: single vessel signals
Grade 2: confluent vessel signals in less than half the area of the synovium
Grade 3: vessel signals in more than half the area of the synovium

4. Hand function by using The Cochin Rheumatoid hand functional scale.

The Cochin scale is a scale to measure functional disability in rheumatoid arthritis (RA) hands. There are 18 questions based on daily activities. The total score was obtained by adding the score of each question rated on a Likert scale from 0 (done without difficulty) to 5 (impossible to do). The first (F1) was activities requiring force and rotation, the second (F2) was activities requiring dexterity and precision, the third (F3) was dynamic activities based on pinching performed with the first 2 or 3 fingers of the dominant hand.

Follow-up was done at end of 8 weeks and 20 weeks. Collected data were checked for completeness and consistency. Statistical analysis was done usingIBM-Statistical Package for the Social Sciences (IBM-SPSS)

Version 21. For descriptive statistics mean, standard deviation and median were used. Continuous variables (age, VAS, DAS-28 ESR, the Cochin hand functional scale) were analysed by student's t-test. Categorical variables (gender, duration of symptoms, grading by using power doppler ultrasound) were analysed using Chi-square test. Within the group comparison (baseline and follow-up data of each group) was done by Repeated measure ANOVA test. Between the group comparison (intervention group and control group) was analysed using student's t-test. A p-value <0.05 was taken as significant.

Ethical approval of the Research Ethics Board, RIMS, Imphal was taken for this clinical study. The study was registered in CTRI with Registration No. CTRI/2021/04/032935.

Results:-

The median age of the participants in years was 36.5. Females were affected more than males in our study. There were no statistically significant difference in between the group comparison of baseline characteristics and baseline dependent variables [Table I,II].

Within the group comparison of mean of VAS, DAS28, Cochin scale, USG Grade from baseline to subsequent follow up at 8 weeks and 20 weeks showed improvement in both the group [Table III].

Between the group comparison in subsequent follow up,there is statistically significant improvement in VAS, DAS 28, USG Grade, Cochin scale, in intervention group in comparisonwith control group at the end of 8 weeks. At the end of 20 weeks, improvement was found to be comparable in both the groups and p-value was not statistically significant [Table IV].

Discussion:-

In our study, within the group comparison of the parameters showed significant improvement in all follow up periods, which is consistent with the fact that triple combination DMARDs is considered the standard treatment of RA. In the first follow up at the end of 8 weeks, between the group comparison showed significant improvement in pain, disease activity and hand function among participants of intervention group. This signifies that there is added effect of intra-articular PRP injection over and above triple combination DMARDs therapy. Tong et al[9] concluded in their study that PRP has anti-inflammatory effects by inhibiting the production of inflammatory factors like IL1b, TNFα and IL6 from MH7A cells and with decrease in inflammation, pain and swelling in the wrist joint subsided and hand function improved. The comparison of semiquantitative USG Grading between the group was found to be statistically significant at the end of 8 weeks. It correlates in the study done in-vitro where it was found that, PRP inhibits angiogenesis related factor expressions in fibroblast like synoviocytes (FLS) cells. Since semi quantitative ultrasound grading was based on the synovium thickening and its vascularity, with decrease in angiogenesis there is decrease in grading.

The patients in our study had improvement in hand function with corresponding decrease in pain and disease activity after intra-articular injection of PRP. In concurrent with the results we found, in a study conducted by Shiveley et al[10], which shows PRP as an adjunct or alternative therapy to DMARDs, they have further mentioned that multitudes of growth factors which is present in PRP when directly injected to inflamed joints, accelerates healing and improves functionality of the patients. Therefore, intra-articular PRP injections in early stages of the disease reduces inflammation and can be administered as an adjunctive to conventional oral DMARDs

In subsequent follow up at end of 20 weeks, there was comparable improvement in both the group with regard to the mean difference in hand function (Cochin Scale) from baseline to 20 weeks follow up. Improvement was more in patients who received intra-articular PRP although not significant, and it suggest that in subjects who were getting triple combination DMARDs, ultrasound guided intra-articular injection of PRP in wrist joint has better beneficialeffects in short term follow up. However, pathophysiological mechanism of deformity in RA is such that, many pro-inflammatory mediators like IL1 and TNFα and degenerative enzymes are expressed resulting in synovial inflammation, cartilage and bone degradation. The disease progression was found to be closely correlated with level of inflammation as reflected by increase in inflammatory markers like ESR and CRP. So targeted treatment by intra-articular injection of PRP to get rid of the inflammation in joints as early as possible is beneficial in prevention of deformity whilst improving hand function.

In a prospective, randomised pilot study conducted by Mochizuki et al[11], intra-articular injection of steroid (Triamcinolone) was effective for pain relief in context of RA in the wrist joint. And in another study conducted by Saif et al[12] comparing the effect of intra-articular PRP vs Steroid, they found that in both groups improvement was comparable at the end of 3 months. From these studies and from the results of our study, we can infer that intra-articular PRP has similar efficacy with steroid in reducing joint inflammation, through its various anti-inflammatory mechanisms and considering the fact that it is safe, and being derived from patients own blood it has very limited side effects as compared to well-known adverse effects of steroids.

Intra-articular injection of PRP in wrist joint was found to be relatively safe. In our study we did not come across any complications. Also, in a systematic review on PRP in management of RA conducted by Chellamuthu et al[13], results showed decrease in disease activity with a good safety profile.

Conclusion:-

Addition of Intra articular PRP in wrist along with DMARDs has early and better improvement in pain and delay disease progression. Intra-articular PRP injection under USG guidance helps in reduction of synovial inflammation and pain, improvement in function and a safe treatment modality. Early treatment and reduction of disease activity by intervention in targeted joint may delay joint deformity and disability. Further studies with larger sample size and longer follow up is recommended to uphold the findings of this present study.

Table I:- Comparisons of background characteristics between the Intra-articular PRP+ triple combination DMARDs (study) and Triple combination DMARDs (control) group (n=50).

Characteristics	**Group**		**p-value***
	Intervention Group n (%)	**Control group n (%)**	
MEDIAN Age in completed years.	34	38	
Mean	37.20+7.90	38.28 + 7.10	0.315
Gender			
Male	11	13	0.571
Female	14	12	
Duration in months			
Less than 3	11	15	
More than 3	14	10	0.688

*Chi-square test, p value <0.05 taken as significant

Table II:- Comparisons of baseline dependent variables between the Intra-articular PRP+ triple combination DMARDs (study) and Triple combination DMARDs (control) group (N=50).

Characteristics	**Group**		**p-value***
	Intervention Group (Mean ± SD)	**Control group (Mean ± SD)**	
VAS	7.60 ± 0.95	7.20 ± 0.913	0.137
DAS 28 ESR	4.13±0.56	4.12±0.44	0.93
USG Grading	2.24±0.57	2.08±0.57	0.73
Cochin scale	61.24 ± 7.1	57.92±5.03	0.063

*Independent t test, p value <0.05 taken as significant

Table III:- Comparison of outcome measures within the groups from baseline to 8 weeks and 20 weeks.

Parameter	**Group (Mean ± SD)**	**Baseline (Mean ± SD)**	**8weeks (Mean ± SD)**	**20 weeks (Mean ± SD)**	**p-value***
VAS Score	Intervention Group	7.6± 0.95	3.56±0.17	4.2±0.2	0.000
	Control group	7.20 ± 0.913	5.16±0.22	3.8±0.25	0.00

DAS 28	Intervention Group	4.13±0.56	2.53±0.12	2.84±0.14	0.000
	Control group	4.12±0.44	3.25±0.09	2.65±0.11	0.00
Cochin Scale	Intervention Group	61.24 ± 7.1	37.36±2.09	38.24±1.9	0.000
	Control group	57.92±5.03	42.0±1.4	35.08±1.7	0.000
USG grade	Intervention Group	2.24±0.57	0.76±0.16	1.52±0.22	0.00
	Control group	2.08±0.57	1.08±0.17	0.32±0.11	0.000

*Repeated measures ANOVA, p value <0.05 taken as significant

Table IV:- Comparisons of mean changes from baseline in outcome measures between Intra-articular PRP + Triple combination DMARDs (Study) and Triple combination DMARDs (Control).

		Intervention Group (Mean ± SD)	**Control group (Mean ± SD)**	**p- value***
VAS Score	8 weeks	4.04±0.88	2.04±1.01	0.00
	20 weeks	3.36±0.99	3.36±1.07	1.00
DAS 28	8 weeks	1.60 ±0 .64	0.86 ± 0.53	0.00
	20 weeks	1.28 ± 0.74	1.47 ± 0.78	0.40
Cochin scale	8 weeks	23.88 ±8.24	15.92 ±6.44	0.00
	20 weeks	23.0 ± 7.47	22.84 ± 8.15	0.94
USG Grade	8 weeks	1.48 ±0.65	1.00 ± 0.76	0.021
	20 weeks	1.04 ± 0.61	1.32 ±0.69	0.135

*Independent t test, p value <0.05 taken as significant

Fig 1:- ACD tubes inside centrifuge machine.

Fig 2:- Ultrasound guided injection of PRP into wrist joint.

Fig 3:- Power doppler ultrasonography of wrist joint to assess grade of inflammation.

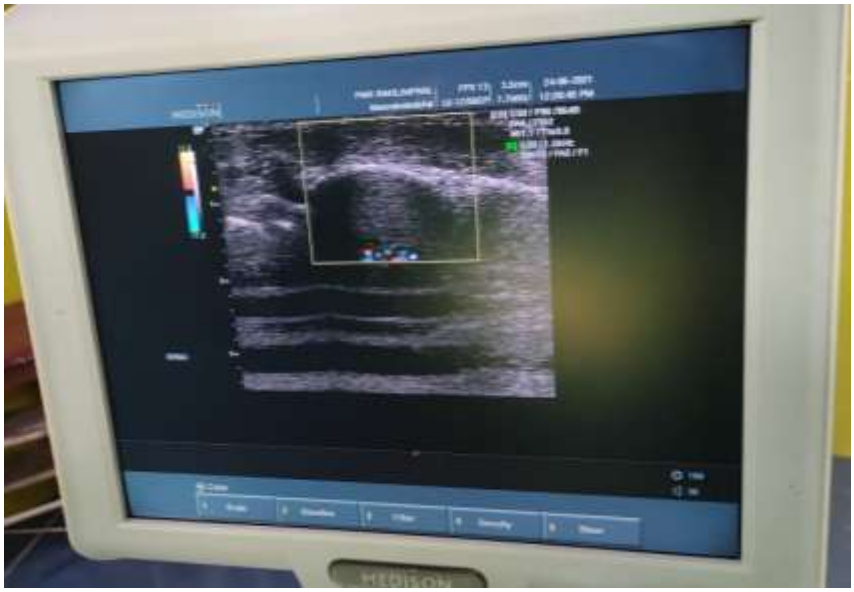

Fig 4:- Changes in signal intensity in power doppler ultrasound

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Conflicts of interest:
None.

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