MEDICAL SCIENCE

The role of PRP as biological stimulator for cartilage regeneration: An experimental prospective study

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ABSTRACT

Introduction: Platelet-rich plasma (PRP) an autologous platelet concentration that contains a large quantity of growth factors is being used to treat an increasing number of articular cartilage injuries and degenerative cartilage lesions. The purpose of PRP is to stimulate cartilage regeneration biologically. *Materials and Methods:* Prospectively enrolled were twelve New Zealand rabbit knees that had received Surgical Phenol Solution-induced osteoarthritis and articular cartilage destruction, followed by platelet-rich plasma therapy-assisted cartilage regeneration. The research was carried out at the Datta Meghe Institute of Higher Education and Research in Sawangi's animal laboratory (Meghe). The study lasted three years. Following two weeks of surgical phenol solution damage on day 1, four groups underwent three treatments of autologous PRP therapy. Rabbits were examined by an open cartilage biopsy and histopathological analysis to determine whether cartilage regeneration had occurred at 3 months. *Discussion:* In terms of tissue morphology, matrix staining, cell distribution, integration of regenerated tissue with subchondral bone, tidemark formation, subchondral bone anomalies and mid/deep zone assessment, group C considerably outperformed groups A and B (P 0.05). Studies on osteoporosis and degenerative cartilaginous tissue have demonstrated that PRP can heal injured tissue. *Conclusion:* In the current experimental research, PRP's potential as a biological stimulator for cartilage regeneration was assessed. This research aimed to expand the role of PRP in improving wound healing outcomes, with a particular emphasis on its effectiveness for skin regeneration. This research will contribute to standardizing the use of PRP in cartilage healing for better results when applied to humans.

Keywords: Osteoarthritis, PRP, Rabbits, Cartilage, Regeneration

1. INTRODUCTION

The harmony between aggressive and protective forces is largely responsible for the appropriate function and preservation of articular cartilage (Harrison,

2005). For the equilibrium between these aspects, biology and its application are crucial (Bendinelli et al., 2010; Heijnen et al., 1999; Civinini et al., 2013). A growing number of articular cartilage injuries and degenerative cartilage lesions are treated using platelet-rich plasma (PRP) is an autologous platelet concentration that includes a significant amount of growth factors (Semple, 2013; Stratz et al., 2012; Nagalla et al., 2011; Farber et al., 2009). These growth factors contribute to the regeneration, repair and acceleration of biochemical processes, which lessens the discomfort brought on by damage to the meniscus and articular cartilage (Ham et al., 2012). Since most mesenchymal repairs result from "controlled" inflammation, it is well-recognised that an inflammatory response of the right size and time is necessary for tissue repair. In this sense, reducing synovial tissue inflammation would result in a decrease in matrix-metalloproteinases, which are enzymes that break down the matrix of the cartilage (Bendinelli et al., 2010).

The intriguing trophic capabilities of PRP are supported by in vitro and preclinical data (Civinini et al., 2013; Zhu et al., 2013), which can be continued with respect to articular cartilage in the presence of specific chondrogenic growth factors, such as PDGF (which may stimulate proliferation and collagen production), TGF-beta (which may enhance chondrocyte synthetic activity, matrix production and cell proliferation and reduces IL-1 catabolic activity) and FGF (which supports various anabolic pathways). Due to cartilage's relatively low capacity for self-repair and its avascular nature (Civinini et al., 2013), the conventional inflammatory repair process does not aid in the healing process when the cartilage is injured because it cannot reach the tissue that is locally impacted.

The use of PRP is justified by the fact that the immediate location of a cartilage injury or illness can enhance the natural healing cascade and tissue regeneration through the supraphysiological release of platelet-derived substances (Bendinelli et al., 2010). In general, data from basic science has shown that PRP can promote the proliferation of chondrocytes and mesenchymal stem cells and deposit type II collagen and proteoglycan (Semple, 2013; Farber et al., 2009). The development of cartilage repair tissue may be accelerated as a result, in principle. PRP contains a lot of platelets, which raises local concentrations of important chemicals and has a long-lasting impact on articular cartilage. Last but not least, when employed in the context of articular cartilage damage, PRP reduces the expression of cyclooxygenase-2 and chemokine-receptor CXCR4 target genes, which may control local inflammation (Krüger et al., 2012).

2. MATERIALS AND METHODS

Twelve New Zealand rabbit knees were prospectively enrolled who had undergone the destruction of articular cartilage with Surgical Phenol Solution and osteoarthritis induced, then regeneration of the cartilage done with help of platelet-rich plasma therapy. The study was conducted at Animal laboratory, Datta Meghe Institute of Higher Education and Research, Sawangi (Meghe).

Study duration

February 2022 to February 2023 – 1 Year

Blood Withdrawal

A 22G to 25G needle or a 22G butterfly linked to a syringe was used to extract up to 5 ml of blood from the auricular marginal veins of both ears of the rabbits. When being handled or subjected to a clinical examination or blood collection, rabbits were readily frightened. Rabbits were therefore contained in a wooden cage. The skin was washed with alcohol before beginning the sample, and the hair on the ear was removed. Due to the sensitivity of the ear's skin, a cream containing lidocaine was used to anaesthetize the area locally. Blood was obtained after gently inserting the needle. To avoid the development of hematomas and blood clots, cotton gauze was firmly pressed to the site of the veno-puncture for at least one minute or until bleeding ceased. Rabbit was monitored for the following several hours to ensure that haemostasis was complete. Auricular marginal veno-puncture was used to take about 5 ml of blood from each ear, which was then split among four test tubes with a combined capacity of 4 ml and CPDA anticoagulant solution.

Preparation of PRP

The tubes were counterbalanced after being put into the centrifuge machine. The first centrifuge cycle was carried out at 220 x g for 20 minutes or at 1200 rpm for 10 minutes (soft spin). Lower red blood cells and upper straw-coloured plasma were extracted from the total blood. To remove straw-coloured plasma from the tubes, a spinal needle connected to a 5ml syringe was moved upward and lower while the draw continued. When an RBC layer was reached or within the first 1 to 2 mm of that layer, the draw ceased. After that, the plasma was expressed into another tube devoid of anticoagulant solution. Other tubes were used in the same way. The plasma-filled tubes were once more centrifuged for 10 or 20 minutes at 480 x g or 2000 rpm. The tube's contents now consist of

an upper layer of clear supernatant serum that contains fibrinogen and platelets in low concentrations and a bottom layer that is frequently reddish in colour and contains highly concentrated platelets.

Research Methodology

After two weeks of day 1 damage by surgical phenol solution, treatment started in 4 groups with autologous PRP therapy, three sessions each in 4 groups

Rabbits x 4 groups

Group A – Control knee

Group B – Every 4th day, three sessions

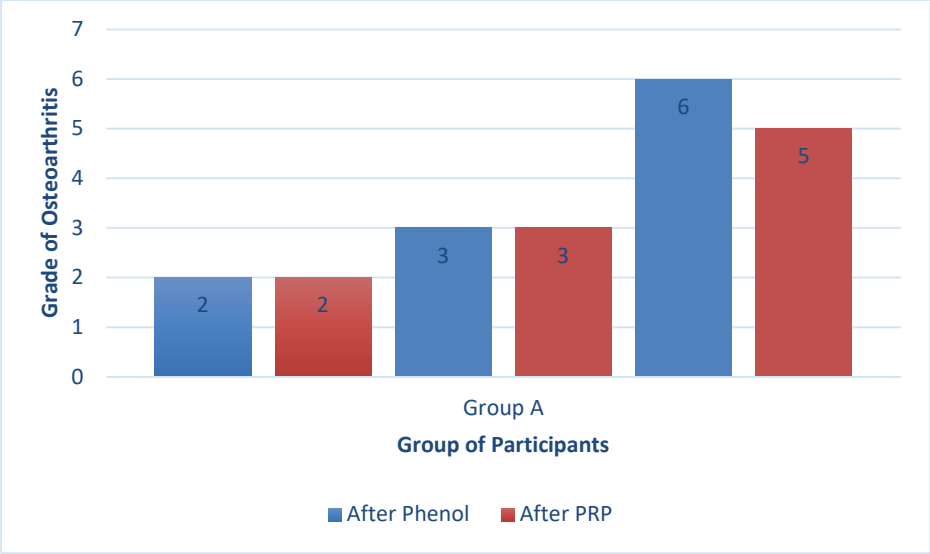
Group C – Every 7th day, three sessions

Group D – On 0, 7 and 21 days

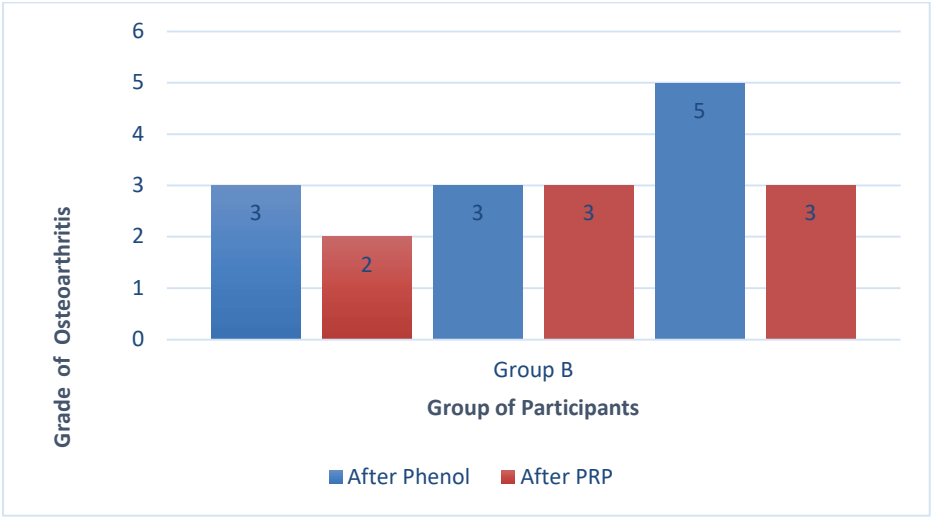
Rabbits were evaluated at three months by taking a cartilage open biopsy and assessed by Histopathological examination to know about cartilage regeneration.

3. RESULTS

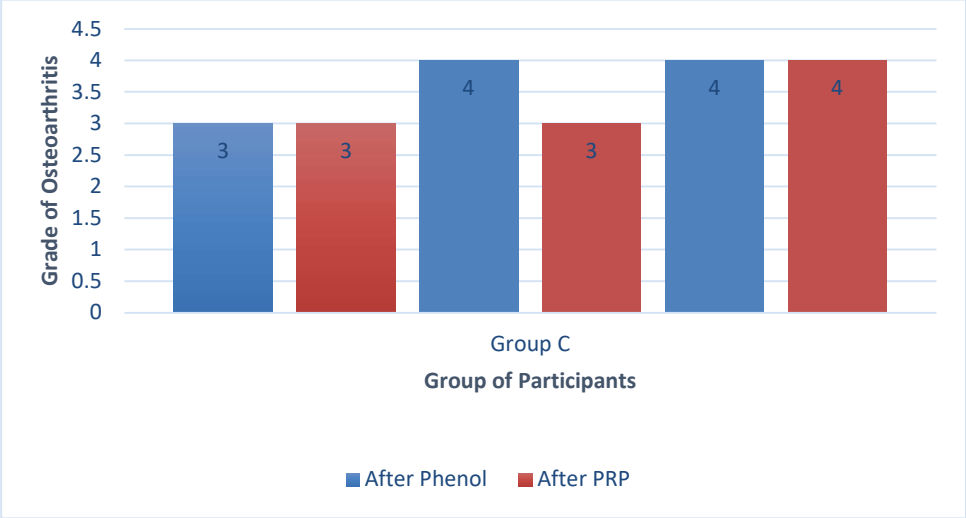
In the present study, the participants, 33.3% of Group A, had Histopathological Grade 2 of Osteoarthritis after Phenol Infiltration (Graph 1). The participants, 33.3% in Group A, had Histopathological Grade 3 of Osteoarthritis after Phenol Infiltration. 33.3% of the participants in Group: A had Histopathological Grade 6 of Osteoarthritis after Phenol Infiltration. The participants, 33.3% in Group B had Histopathological Grade 2 of Osteoarthritis after Phenol Infiltration. The participants 66.7% in Group B had Histopathological Grade 3 of Osteoarthritis after Phenol Infiltration (Graph 2). 33.3% of the participants in Group B had Histopathological Grade 5 of Osteoarthritis after Phenol Infiltration. The participants, 33.3% in Group C, had Histopathological Grade 3 of Osteoarthritis after Phenol Infiltration. The participants 66.7% in Group C had Histopathological Grade 4 of Osteoarthritis after Phenol Infiltration (Graph 3). The participants, 33.3% in Group D, had Histopathological Grade 2 of Osteoarthritis after Phenol Infiltration. The participants, 33.3% in Group D, had Histopathological Grade 3 of Osteoarthritis after Phenol Infiltration. 33.3% of the participants in Group D had Histopathological Grade 6 of Osteoarthritis after Phenol Infiltration (Graph 4).



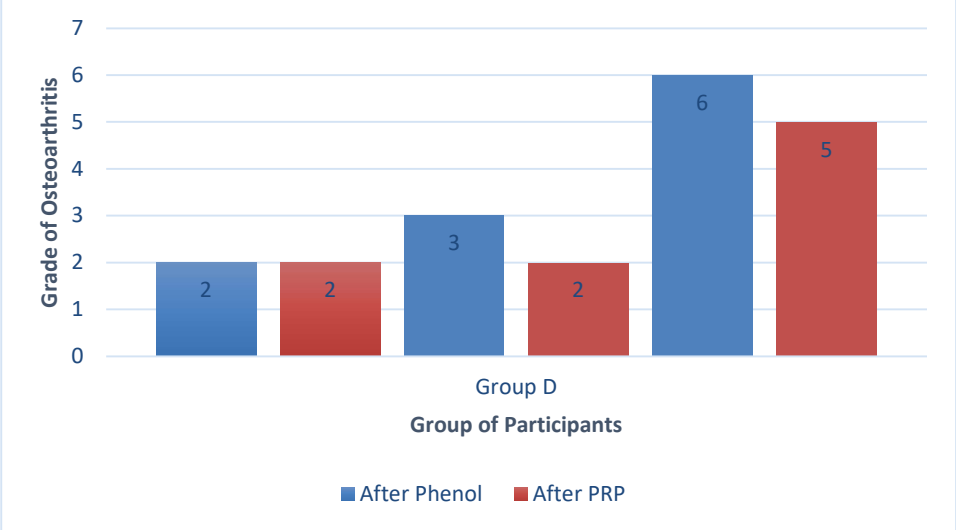
Graph 1 Association Between Group and Histological Grade of Osteoarthritis After Phenol and PRP Infiltration



Graph 2 Association Between Group and Histological Grade of Osteoarthritis After Phenol and PRP Infiltration



Graph 3 Association Between Group and Histological Grade of Osteoarthritis After Phenol and PRP Infiltration



Graph 4 Association Between Group and Histological Grade of Osteoarthritis After Phenol and PRP Infiltration

In our study after two weeks of day 1 damage by surgical phenol solution, treatment started in 4 groups with autologous PRP therapy, three sessions each in 4 groups (Figure 1, 2, 3).

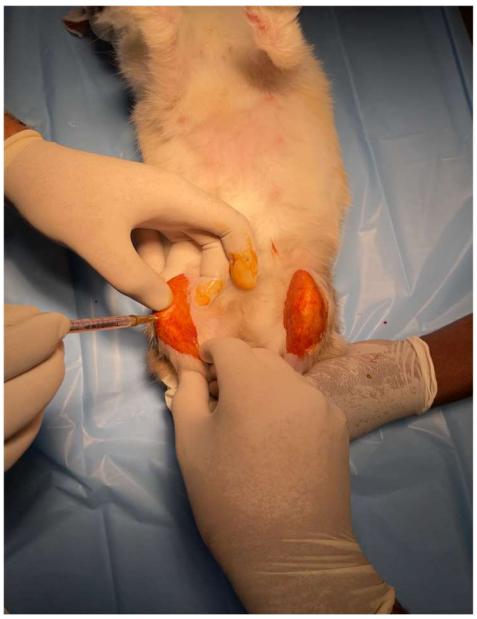


Figure 1 Surgical Phenol Solution Infiltration in Knee Joint

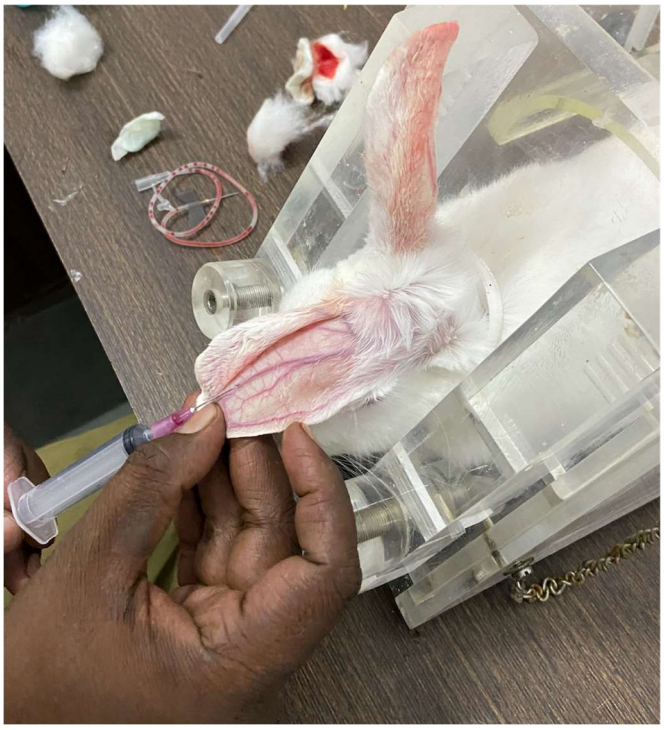


Figure 2 Collection of blood from ear for preparation of PRP

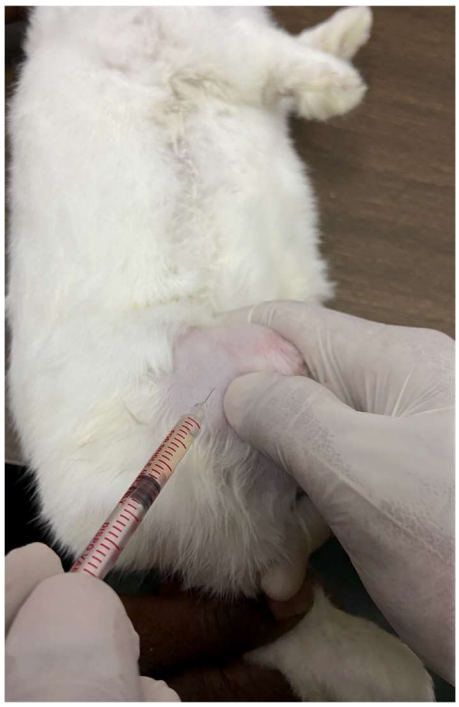


Figure 3 Infiltration of PRP in Knee Joint

Rabbits were evaluated at three months by taking a cartilage open biopsy (Figure 4, 5) and assessed by Histopathological examination to know about cartilage regeneration (Figure 6, 7, 8, 9, 10).

Figure 4 Open Biopsy for Cartilage Sample

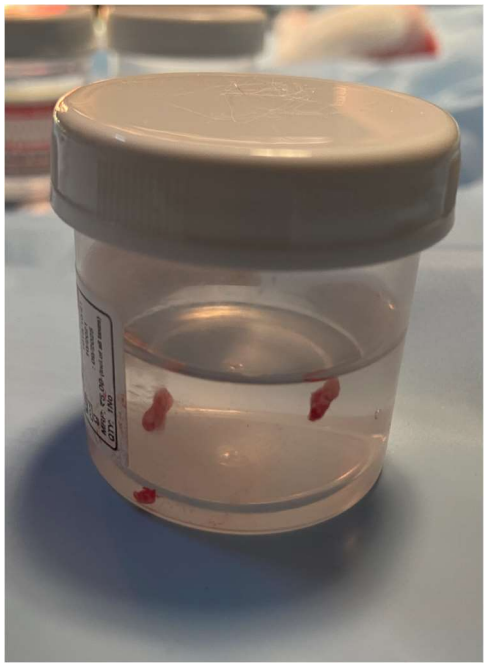


Figure 5 Cartilage Sample

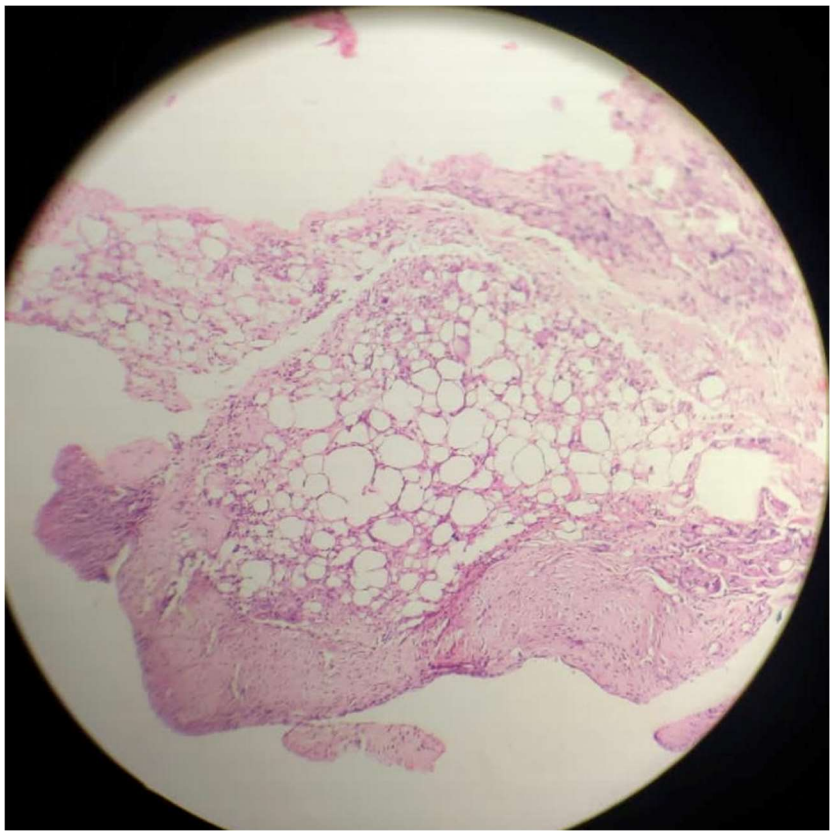


Figure 6 Chondrocytes Degeneration (Group A)

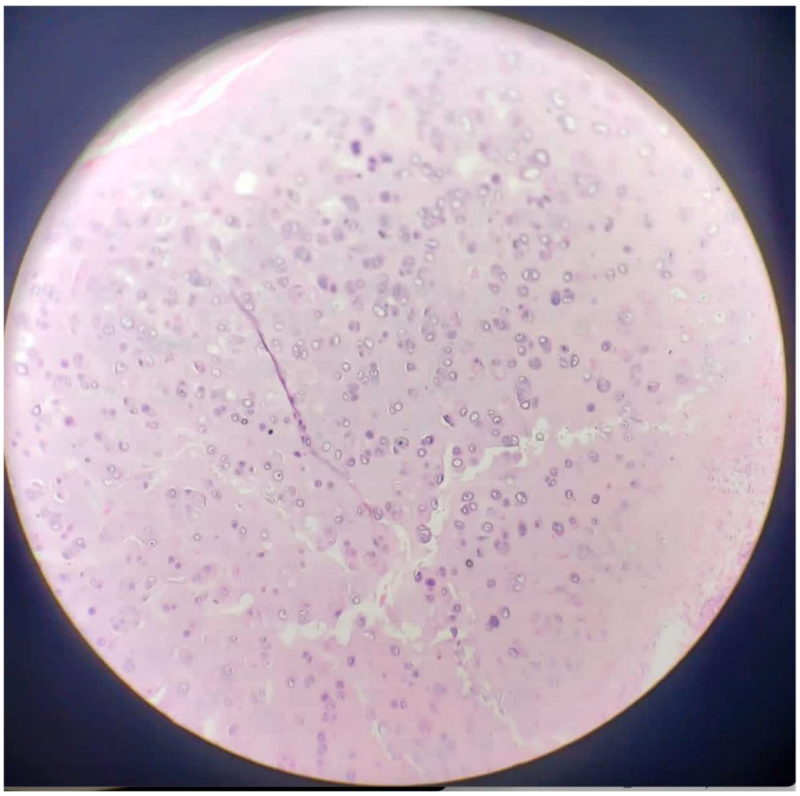


Figure 7 Chondrocytes Proliferation and Regeneration (Group B)

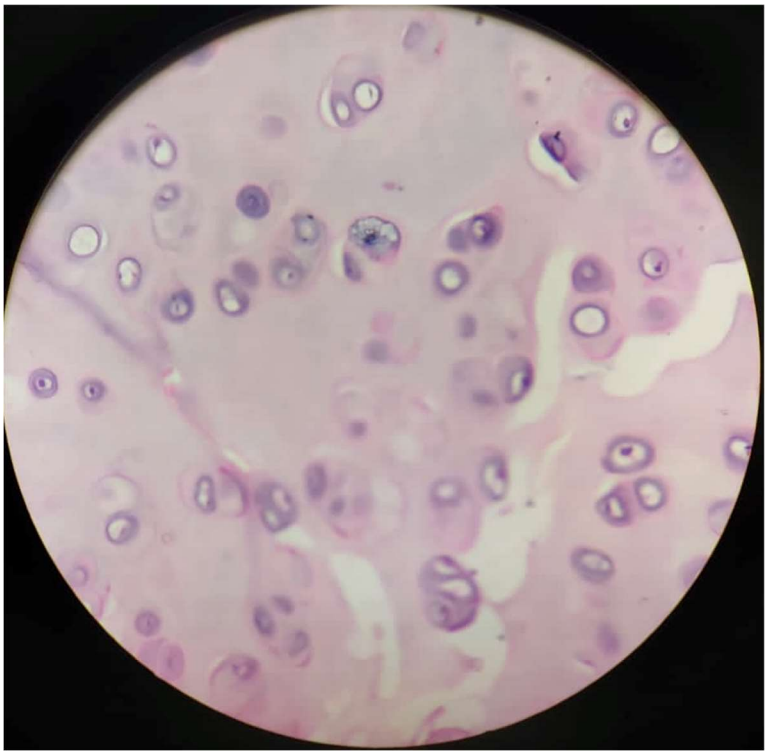


Figure 8 40x image of Chondrocytes

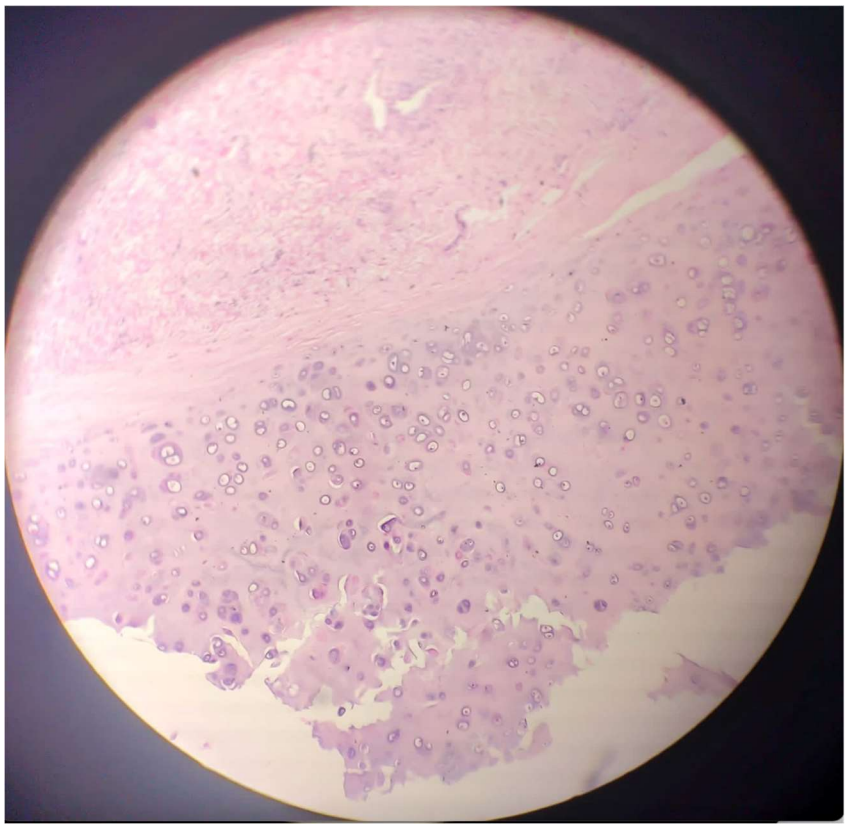


Figure 9 Cartilage Regeneration (Group C)

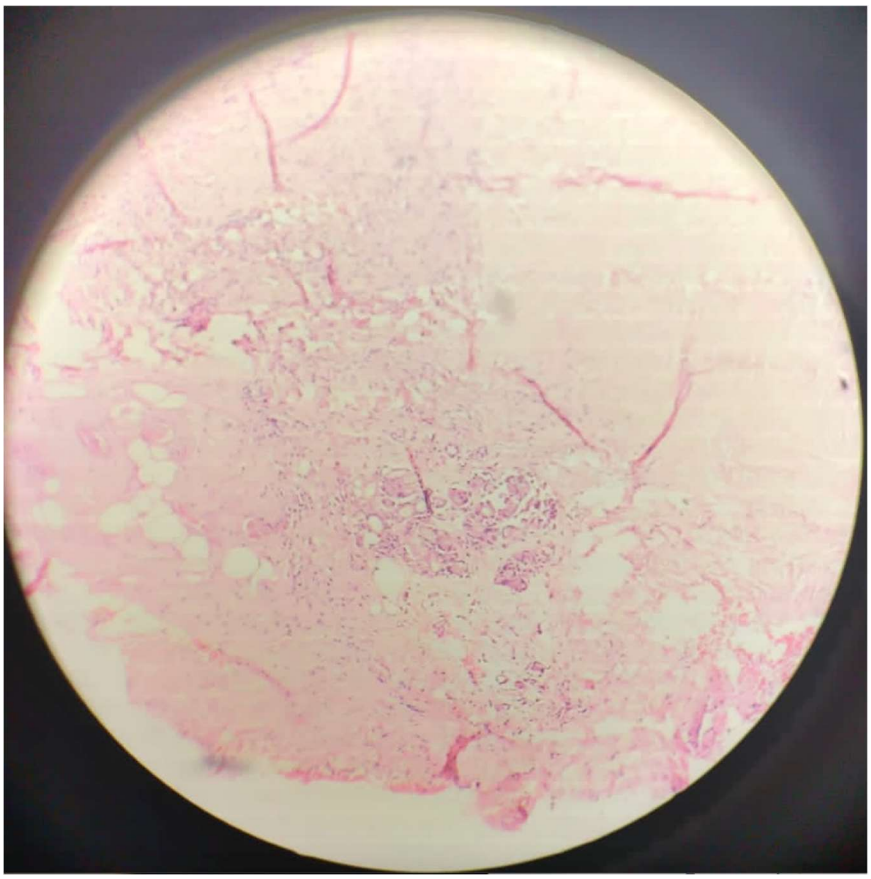


Figure 10 Cartilage Regeneration (Group D)

Compared to groups A and B, group C had significantly higher mean histology ratings for tissue morphology, matrix staining, cell distribution, integration of regenerated tissue with subchondral bone, tidemark formation, subchondral bone anomalies and mid/deep zone assessment (P 0.05). Even though group B had better marks, there was no discernible difference between group A and group B. Groups C and B scored considerably higher for vascularity in the restored tissue than group A (P 0.05). Although group C had a higher score, it did not substantially differ from group B's (Table 1, 3, 4, 5, 6, 7).

In our study the best results were seen in Group B in terms of regeneration of chondrocytes than other groups. Hence PRP infiltration every 4th day is more preferred for infiltration as it matches with the healing cycle (Table 2).

Table 1 Cartilage parameters for assessment of Cartilage Regeneration

Tissue Morphology***	0.00 ± 0.00	1.67 ± 0.58	1.00 ± 0.00	1.67 ± 0.58	0.034[2]
Matrix Staining***	0.00 ± 0.00	1.33 ± 0.58	1.00 ± 0.00	1.33 ± 0.58	0.039[2]
Cell Distribution	0.33 ± 0.58	1.23 ± 0.58	1.00 ± 1.00	0.63 ± 0.58	0.046[2]
Surface Architecture	0.00 ± 0.00	1.33 ± 0.58	0.33 ± 0.58	1.00 ± 1.00	0.015[2]
Integration with adjacent bone	0.67 ± 0.58	1.33 ± 0.58	0.33 ± 0.58	0.67 ± 0.58	0.274[2]
Formation of Tidemark	0.33 ± 0.58	1.33 ± 0.58	0.67 ± 0.58	0.33 ± 0.58	0.216[2]
Subchondral bone abnomality	0.00 ± 0.00	0.33 ± 0.58	0.33 ± 0.58	0.33 ± 0.58	0.748[2]
Abnormal Calcification	0.67 ± 0.58	1.00 ± 1.00	0.33 ± 0.58	0.67 ± 0.58	0.725[2]
Vascularization in repair tissue	0.33 ± 0.58	1.33 ± 0.58	1.33 ± 0.58	0.67 ± 0.58	0.165[2]
Total Score***	2.33 ± 2.08	11.00 ± 3.00	6.33 ± 1.53	7.33 ± 1.53	0.033[2]

****Significant at p<0.05, 2: Kruskal Wallis Test*

The following variables were significantly associated (p<0.05) with the variable 'Group': Regeneration of Chondrocyte after PRP infiltration, Tissue Morphology, Matrix Staining, Cell Distribution, Surface Architecture, Total Score. Fisher's exact test was used to explore the association in variables between 'Group' and 'Histopathological Grade and Stage of Osteoarthritis after Phenol and PRP Infiltration', Regeneration of chondrocyte after PRP infiltration, infection after open biopsy procedure more than 20% of the total number of cells had an expected count of less than 5. In the four subgroups of the variable group, the variables like Histopathological Score of Osteoarthritis after Phenol and PRP Infiltration, weight, age of the rabbit, Platelet Count (In Lacs), Leucocyte Count, Tissue Morphology, Matrix Staining, Cell Distribution, Surface Architecture, Integration with Adjacent Bone, Formation of Tidemark, Subchondral Bone Abnormality, Abnormal Calcification, Vascularization in repair tissue were not normally distributed. Thus, to compare these groups, non-parametric tests (Kruskal Wallis Test) were employed.

Table 2 Association Between Group and Regeneration of Chondrocyte after PRP infiltration (n = 12)

Regeneration of Chondrocyte after PRP infiltration	Group					Fisher's Exact Test	
	A	B	C	D	Total	χ2	P Value
Not Seen	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (25.0%)	12.000	0.018
Seen	0 (0.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	9 (75.0%)		
Total	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	12 (100.0%)		

There was a significant difference between the various groups in terms of distribution of Regeneration of Chondrocyte after PRP infiltration (χ2 = 12.000, p = 0.018).

Table 3 Comparison of the 4 Subgroups of the Variable Group in Terms of Tissue Morphology (n = 12)

Tissue Morphology	Group				Kruskal Wallis Test	
	A	B	C	D	χ2	p value
Mean (SD)	0.00 (0.00)	1.67 (0.58)	1.00 (0.00)	1.67 (0.58)	8.643	0.034
Median (IQR)	0 (0-0)	2 (1.5-2)	1 (1-1)	2 (1.5-2)		
Min - Max	0 – 0	1 - 2	1 - 1	1 - 2		

Table 4 Comparison of the 4 Subgroups of the Variable Group in Terms of Matrix Staining (n = 12)

Matrix Staining	Group				Kruskal Wallis Test	
	A	B	C	D	$\chi 2$	p value
Mean (SD)	0.00 (0.00)	1.33 (0.58)	1.00 (0.00)	1.33 (0.58)	8.360	0.039
Median (IQR)	0 (0-0)	1 (1-1.5)	1 (1-1)	1 (1-1.5)		
Min - Max	0 – 0	1 - 2	1 – 1	1 - 2		

Table 5 Comparison of the 4 Subgroups of the Variable Group in Terms of Cell Distribution (n =12)

Cell Distribution	Group				Kruskal Wallis Test	
	A	B	C	D	$\chi 2$	p value
Mean (SD)	0.33 (0.58)	1.23 (0.58)	1.00 (1.00)	0.67 (0.58)	3.239	0.046
Median (IQR)	0 (0-0.5)	1 (1-1.5)	1 (0.5-1.5)	1 (0.5-1)		
Min – Max	0 – 1	1 - 2	0 – 2	0 - 1		

Table 6 Comparison of the 4 Subgroups of the Variable Group in Terms of Surface Architecture (n = 12)

Surface Architecture	Group				Kruskal Wallis Test	
	A	B	C	D	$\chi 2$	p value
Mean (SD)	0.00 (0.00)	1.33 (0.58)	0.33 (0.58)	1.00 (1.00)	5.928	0.015
Median (IQR)	0 (0-0)	1 (1-1.5)	0 (0-0.5)	1 (0.5-1.5)		
Min – Max	0 – 0	1 - 2	0 - 1	0 - 2		

Table 7 Comparison of the 4 Subgroups of the Variable Group in Terms of Total Score (n = 12)

Total Score	Group				Kruskal Wallis Test	
	A	B	C	D	$\chi 2$	p value
Mean (SD)	2.33 (2.08)	11.00 (3.00)	6.33 (1.53)	7.33 (1.53)	8.715	0.033
Median (IQR)	3 (1.5-3.5)	11 (9.5-12.5)	6 (5.5-7)	7 (6.5-8)		
Min – Max	0 – 4	8 - 14	5 - 8	6 - 9		

4. DISCUSSION

In vitro and preclinical studies suggested the idea of utilisation of PRP in cartilage surgery due to its trophic effects and ability to help mesenchymal stem cells differentiate into bone and cartilage under the right circumstances (Yamada et al., 2004). Another study on human PRP found that collagen synthesis in osteoblasts increased (García and Reyes, 2005). Some studies have demonstrated that, in this combination, calcium sulphate acts as an activator of platelets and a delivery system for the platelet-released growth factors (Hildner et al., 2011; Pritzker et al., 2006). So, it's possible to say that platelets' endogenous growth factors aid in the healing process.

Pritzker et al., (2006) emphasized a particular feature of the OARSI system that can distinguish the differences between early or mild OA (grades 1e3). The OARSI criteria for OA histopathology assessment appear superior to earlier techniques at this early stage. The OARSI Cartilage Histopathology Grading/Staging System is a traditional instrument with substantial potential to become a standard tool for OA cartilage histopathology grading; however, more evaluation will be necessary.

The Weight of Rabbit (Kgs) in Group: B ranged from 1.3 - 1.7. The Weight of Rabbit (Kgs) in Group: C ranged from 1.8 - 2.5. The Weight of Rabbit (Kgs) in Group: D ranged from 1.4 - 2.1. In a study by Manafi et al., (2012), 15 young and healthy New Zealand male rabbits were taken in this experimental study, each at five months of age and weighing between 2 to 2.5 kg.

There was a significant difference between the four groups in terms of Surface Architecture ($\chi 2 = 5.928$, $p = 0.015$), with the mean Surface Architecture being highest in the B group. In a study by Xie et al., (2014), chondrocytes were cultured either on the two-dimensional surface of fibrin scaffolds or in three-dimensional scaffolds. Compared to controls without the addition of exudate, the supernatant from platelet-rich fibrin (PRF) up regulated the mRNA expression of Col II and aggrecan. It boosted the production of glycosaminoglycan and proteoglycan. At six months, both treatment groups had successfully integrated the chondral surface. However, the PRP-treated Group had only partially formed the bone and had irregularly incorporated the cartilage surface.

However, the Group that received the scaffold showed considerably greater osteochondral repair. A full defect fill and surface congruity with native cartilage were visible on the MRIs of three patients.

Studies on degenerative cartilaginous tissue and osteoporosis have shown that PRP can repair damaged tissue (Oliver et al., 2015; Sheu et al., 2020; Fortier et al., 2010). Mesenchymal stem cells (MSCs) in BMAC suggest that they may have significant regenerative properties, even for avascular tissues like articular cartilage. This is because MSCs can signal the surrounding tissue to secrete growth factors that regulate the immune response and promote regeneration at the injury site. BMAC has also been reported to contain increased levels of the growth factors interleukin one receptor antagonist (IL-1RA) and interleukin 1-beta (IL-1), which play crucial roles in regeneration through immune response modulation in the joint space (Hildner et al., 2010; Chen et al., 2014).

5. CONCLUSION

The present experimental study evaluated the role of PRP as a biological stimulator for cartilage regeneration. This study included healthy rabbits of weight more than 1 kg who had undergone the destruction of articular cartilage and inducing osteoarthritis, then regeneration of the cartilage using platelet-rich plasma (PRP) therapy. Rabbits were evaluated at three months by Histopathological examination for cartilage regeneration and only acute destruction of cartilage was included in this study. It has been concluded that there was a significant difference between the four groups in terms of tissue morphology, Matrix Staining, Cell Distribution, Surface Architecture and Total Score. This study intended to broaden the role of PRP towards improving outcomes of wound healing, particularly with the focus on its efficiency for skin regeneration. This study will help to standardize the role of PRP in cartilage regeneration for human usage and improved outcomes.

Acknowledgement

We thank the subjects who were all contributed samples to the study.

Ethical approval

The study was approved by the Institutional Animal Ethics Committee of Datta Meghe Institute of Higher Education and Research (Ethical approval code: DMIMS (DU)/IAEC/2019-20-10).

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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