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Efficacy of PRP in Knee Osteoarthritis- Alternative Option to Conventional Line of Treatment.

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Abstract: *PRP (platelet rich plasma) is new modality for management of Knee Osteoarthritis.According to published randomised clinical trials data, it shows that PRP will be definitely strong Alternative for Conventional management of Knee osteoarthritis. Intraarticular PRP injection shows better outcome in young, active, low grade osteoarthritis compare to hyaluronic acid. It need to be standardised protocol for PRP preparation, conduct high grade randomised clinical trials. Intraarticular PRP injection shows promising result after 3 months onwards, PRP treatment is Efficacious without encountering side effects.*

Key words*: Platelet rich plasma, osteoarthritis, Intraarticular, injections, regenerative medicine.*

BACKGROUND

OA is known as degenerative arthritis, causes articular cartilage & subchondral bone abnormalities. A causes moderate to severe deformity in 43 million people globally, one in every two people may develop symptomatic OA up to the age of 85 years(1,2).Articular cartilage damage causes poor healing potential & OA(3).so to prevent cartilage damage, enhance healing process, prevent morbidity by any means is interested modality for patients & medical specialities.in that way nonoperative & effective treatment modalities gain waitage which come under umbrella of regenerative medicine(4).Intraarticular PRP injection for OA shows promising treatment option in last decades(5).

PRP has platelet (PLT) count above normal baseline platelet count(6).it was injected back to damaged area, GF in PRP promote healing(7). Autologous nature of PRP theoretically reduces potential side effects (8, 9).

Numerous studies demonstrated PRP efficacy in tendinopathy & ligamentous injuries (10-16). Up to date, multiple randomised clinical trials shows promising result in elbow lateral epicondylitis (tennis Elbow) (17-19).

Many variables are play important role in PRP clinical application. Preparation method, needle gauge, platelet count, leucocyte count, anaesthetic use, volume of PRP, number of injections.

PREPARATION METHOD

To separate PRP centrifuge or density gradient method mostly used (20,21).first spin separate Red blood cells & leucocytes, platelets (buffy coat) from whole blood as cellular blood component ,second spin further concentrate PLT & leucocytes. Number of centrifugation, speed/time play major role in concentration of Platelet & leucocytes (22, 23).

PROCEDURES (24, 25)

PRP method

1. Take WB (whole blood) in acid citrate dextrose tube.

2. Do not chill WB during procedure.

3. Do centrifugation soft spin.

4. Separate WB in three layers bottom of tube RBC, uppermost PPP (platelet poor plasma) contain platelet, WBC, intermediate buffy coat which contain high number of platelet, leucocytes.

5. Collect PPP & buffy coat in separate sterile tube.

6. Centrifuge at higher “g” called hard spin.

7. Platelet pellet formed at bottom of tube, discard upper 2/3 & dissolve pellet in lower 1/3.

8. Resultant is concentrated PRP.

Buffy coat Method

1. Take WB in ACD tube by venepuncture

2. Centrifuge at optimum speed /time.

3. Three layers formed uppermost PPP, intermediate Buffy coat, lowermost RBC in tube.

4. Collect buffy coat & transfer in separate sterile tube.

5. Centrifuge at low speed to separate WBC or used leucocyte separation filter.

PLT COUNT IN PRP

Platelet count in PRP preparation method & its clinical application is always debate issue. Mishra et.al (26) proposed classification of PRP according to PLT count, high (>5x PLT), low (<5x PLT).especially in knee OA low platelet count PRP also shows promising result. Some author suggest double PLT count in PRP for good clinical outcome. Published literature shows 8 times of PLT in PRP compare to baseline normal blood shows good result (21, 27).

In clinical practise evidence shows (2-3x BL) in knee OA gives good clinical outcome (23, 28-31).scientific evidence are currently limited regard to PRP PLT for knee OA.

Key data in Knee Osteoarthritis

Concentration of soluble mediators released by Platelet interact with synovial membrane, synovial fluid, cartilage, subchondral bone & initiate to repair damaged, promote healing.

Chondrocytes & extracellular matrix

In most available in vitro clinical studies , animal & human chondrocytes are proliferated by PRP(32-34).PRP may promote recruitment of mesenchymal stem cells (MSC),their adhesion ,proliferation & differentiation into Chondrocytes(35,36).anabolic effect of chondrocytes in proteoglycans & collagen type II synthesis was found in some in vitro studies & in animal models(37,38).

Long term studies in large sample of human model & animal model need to be carried out for conclusion.

Synoviocytes & Synovial fluid

Osteoarthritis is crosstalk between cartilage & synovial membrane (39).during knee arthroplasty for osteoarthritis , PRP promotes production of hyaluronic acid by type B synoviocytes(40).HGF (hepatocyte growth factor) produced by PRP & Synoviocytes limit inflammatory procedures in synovial membrane(40-42).

Angiogenesis & Joint Inflammation

PRP contains proangiogenic growth factors (PDGF, VEGF, FGF, and TGF) that may play role in healing process after damaged to tendon & muscle fibre (43). Uncontrolled angiogenesis trigger inflammation process especially by VEGF & TGF in knee Osteoarthritis. Several in vitro study shows no increase in VEGF & TGF by PRP.

Controlled Angiogenesis despite Proangiogenic growth factors contain by PRP is probably due to release of mediators of Angiogenesis inhibitor thrombospodin 1 & platelet factor 4(44, 45).

Some PRP components have pro inflammatory effect such as TNF, IL & proteins contain in α granules like 2 macroglobulin & vitamin D binding proteins (45).

This anti-inflammatory mechanism most probably involve inhibition of NF-KB pathway which is key pathway of pathogenesis of Osteoarthritis (46). Production of IGF & HGF by Synoviocytes are potent inhibitor of NF-KB pathway (47).

PRP IN KNEE OSTEOARTHRITIS

A literature review (48) identified 20 open label studies which shows efficacy in pain & function in knee osteoarthritis. Limitation of this study involves heterogeneity of population, number of PRP injections, interspacing between two injections, volume of PRP, underlined Platelet count, leucocyte count. Follow up is not more than 1 year. Same group of people perform different trials.

One study shows effect of PRP on structural & functional improvement in Knee Osteoarthritis with monitoring by magnetic resonance imaging (MRI) in 73 % patients (49).the study design has some drawbacks number of patients are 20 only. To conclude final verdict need to be carryout randomised controlled trials, on the basis of available data of randomised clinical trials, no one trial compare with intraarticular corticosteroid injections which is routine line of treatment for knee osteoarthritis.

A single randomised controlled trial compare with placebo (Intraarticular saline injection)(50),78patients included in trails ,they have both knee Osteoarthritis ,allocated for single PRP injection, Two PRP Intraarticular injection, single & two saline injection. Pain & functional improvement was observed in both PRP group with

statistically improvement in VAS score & WOMAC domain. Exacerbation of pain occurred in double & single PRP injection group (44% versus 22% in single PRP, P<0.05).

The five randomised clinical trials was conducted with comparison of hyaluronic acid Intraarticular injections, study design includes 100 patients in each clinical trials monitoring tool includes VAS score, WOMAC domain, Pain & functional improvement, there was a week interval between two PRP or hyaluronic acid injections .statistical data are variable may be due to lies in different preparation method of PRP, platelet count, leucocyte count, volume (51).

In first study(52) ,PRP compare with hyaluronic acid , 60 patients included in each group ,four injections of PRP & hyaluronic acid was given ,VAS ,WOMAC score was calculated in 4,12,24 weeks. Osteoarthritis (kellgren grade 1 to 3) were included in study. Statistical improvement was seen in both groups but in PRP groups after 12 & 24 weeks improvement was better compare to hyaluronic acid group.

In second study (53) ,55 patients included , PRP Intraarticular injection Was compared with Hyaluronic acid injection , IKDC score,KOOS, motion range was determined at 4,12,24 weeks ,no significant improvement was noted but symptomatic relief in both group was noted.

A third study (54) recruit patients from three different centres, used PRP, low molecular weight hyaluronic acid, high molecular weight hyaluronic acid intraarticular injections. IKDC, VAS pain score after 2 months statistically improved in PRP &low molecular weight Hyaluronic acid group compare to high molecular weight hyaluronic acid group. But after 6 months improvement in symptom relief were noted in PRP group.

Fourth trials (54) included 176 patients, three injections of PRP (5 fold increase to normal blood platelet count) & hyaluronic acid were given at 1 week apart, primary outcome noted in WOMAC score reduction at 24 weeks. Secondary outcome noted in ORSI response rate, lequesne index. The primary outcome measure shows significant improvement in PRP group ((34% ± 38% vs. 21% ± 24% of responders, P = 0.05).no statistical improvement noted in secondary outcome.

Final trial, recruit 60 patients in PRP group (4 fold Increase in platelet compare to baseline), 60 patients in hyaluronic acid group, three injections each given & VAS pain score, WOMAC compare at 4, 12, 24 weeks. After 3 months VAS pain score & WOMAC total score improvement were observed in PRP group significantly & last after 6 months also.

DISCUSSION

PRP intraarticular injection is non operative means of knee Osteoarthritis management .according to literature, randomised controlled trials, shows prognostic outcome in symptomatic knee OA with PRP intraarticular injections. It was show that PRP has better outcome compare to hyaluronic acid intraarticular injection. Kellgren grade 1 -3 OA patient <50 yrs. old shows significant improvement in VAS pain score, WOMAC total score & symptomatic improvement. It was shown that PRP has sustain result after 6months as well. Up to data, statistical data is insufficient, need to be carried out multicentre randomised clinical trials with large number of patients. Intraarticular Steroid injection is primary & popular nonoperative conventional line of treatment in orthopaedic umbrella. It need to be carried out clinical trial study of PRP in comparison with intraarticular steroid.PRP will be good alternative nonoperative option for management of Knee OA in young age group .

There are different subtypes of PRP, WBCs reached PRP is one important subtypes. Leucocytes are important part of WBCs, excessive leucocytes infiltration associated with chronic inflammation & delayed wound healing. Through phagocytosis macrophages clear particulate debris that accumulate after neutrophil activation & released proteolytic enzymes (55).

Several studies shows result of Leucocyte rich PRP Versus Leucocyte poor PRP ,leucocyte rich PRP trigger acute inflammation & causes Synoviocytes cell death(56,57).apart from safety profile, leucocyte rich PRP & leucocyte Poor PRP shows transient reaction compare to HA(58).according to available data, no direct comparative study conducted between leucocyte rich PRP & leucocyte poor PRP to evaluate efficacy ,safety ,treatment outcome in clinical patient management. This is important topic to study.

CONCLUSION

In knee OA, PRP is promising treatment modality. It will shows better outcome than HA in young age group patient of Kellgren grade I to III. Efficacy & safety issues are not biased with intraarticular PRP injection for Knee OA. Minor side effect like post injection pain, swelling reported that resolve in 2 to 3 days. No major long term consequences noted till date. Result sustain after 6 months also. Need to carry out comparative study with steroid, to

standardise preparation method for clinical application in future.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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