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Comparative study between platelet rich plasma (PRP) injection versus radiofrequency for treatment of patients with chronic knee osteoarthritis

Shawky Mohamed Shawky Abdel Galil*[1], Ahmed Elsaied Abdelrahman[2], Huda F. Ghazaly[1], Mohamed Kamel Ahmed Hasanen[1]

[1]Departments of Anesthesia and Intensive Care, Faculty of Medicine - Aswan University, Egypt

[2]Departments of Anesthesia and Intensive Care, Faculty of Medicine - Sohag University, Egypt

***Corresponding author:** Shawky Mohamed Shawky, **E-Mail:** shawky_1184@yahoo.com

ABSTRACT

Background: Knee osteoarthritis (OA) is considered as one of the main causes of functional disability. The patient with OA is suffering not only from the persistent pain, stiffness and limited mobility. Treatment of knee OA is platelet-rich plasma (PRP). Although PRP is one of the options in the management of knee OA, its effectiveness and wide application is still controversial. On the other hand, the use of radiofrequency ablation (RFA) procedures to treat chronic knee pain has surged in the past decade. Accepted targets for RF treatment now include most neural structures to include major nerves and ganglia.

Objective: To compare the pain-relieving effect of radiofrequency of genicular nerve versus PRP if injected in the intra-articular osteoarthritic knee joint.

Patients and methods: The present prospective, comparative, randomized study was conducted at Aswan university hospital. Fifty patients with knee osteoarthritis were included during 6-month period. Studied populations were divided into 2 groups: **Group I:** Which included 25 patients who received a single intraarticular injection of PRP only. The mean age of the included patients was 53.23 ± 8.03 years and the majority of them were females (80%). The mean BMI was 28.43 ± 2.11 Kg/m^2, and **Group II:** Which included 25 patients who received a single session of conventional radiofrequency of genicular nerves. The mean age of the included patients was 56.04 ± 7.58 years and the majority of them were females (76%). The mean BMI was 29.61 ± 1.64 Kg/m2

Results: Our analysis showed that the PRP did not significantly improve the VAS score (p =0.28). Regarding the effect of radiofrequency of genicular nerve on study outcomes, we found that radiofrequency of genicular nerve significantly improved the VAS score (p =0.09). In terms of comparison analysis, we found that there were statistically significant differences between the included groups in terms of VAS score (p =0.63), at the end of follow-up. The radiofrequency of genicular nerve group showed statistically significant lower values than the PRP alone group.

Conclusion: Radiofrequency of genicular nerve is an effective modality in reducing the pain and improving the mobility of the knee in patients with knee osteoarthritis in patients who are no responder to pharmacological treatment.

Keywords: Platelet rich plasma (PRP) injection, Radiofrequency, Chronic knee osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is one of the most common musculoskeletal diseases of elderly people. OA is among the 10 considerable causes of disability in the overall global population **(1).**

There are two types of OA: primary, due to unknown cause, and secondary as occurs with trauma or other rheumatic, endocrine, metabolic and congenital disorder **(2).**

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Knee OA has become a worldwide health issue, ageing of the population and increasing prevalence of obesity are associated with increasing prevalence of knee OA. Therefore, the need for efficacious, reliable and cost-effective treatment modalities have been emphasized [(3)].

Current approaches for the treatment of knee osteoarthritis (OA) are mainly symptomatic, the target in treating patients with OA should be the safest possible intervention, with the best pain relief and prevention of further functional disability. Many treatment options are present like weight reduction, pharmacological treatment, non-surgical procedures and surgery [(4)].

There is a distinct need for new procedures that are cost effective by reducing the need for pharmaceutical and surgical management, while targeting the biochemical process of OA. One of the experimental ortho-biological treatments include platelet-rich plasma (PRP) injection therapy [(5)].

Platelet-rich plasma (PRP) is a natural concentrate of autologous growth factors obtained through centrifugation of a patient's own blood. PRP is obtained at a low cost and in a simple and minimally invasive manner. Bioactive cytokines and proteins from the platelet's alpha granules induce chemotaxis, cellular migration, proliferation, differentiation and extracellular matrix production [(6)].

In addition, these proteins increase the release of angiogenic growth factors contributing to tissue regeneration and growth, the main growth factors contained in PRP are platelet-derived growth factor (PDGF), transforming growth factor β (TGF β), insulin-like growth factor (IGF-1) and fibroblast growth factor (FGF). Interestingly, these factors have been involved in chondrogenesis and cartilage regeneration [(7)].

These growth factors stimulate cell proliferation, migration, differentiation and matrix synthesis and can affect chondrocyte metabolism, chondrogenesis and improve cartilage healing in vivo [(8)].

Another method for treatment of knee osteoarthritis is radiofrequency. Radiofrequency neurotomy is used to improve functioning and relieve pain by destroying nerves innervating painful tissue or by disturbing the transmission of pain signals, genicular nerves supplying the knee region include obturator, femoral, saphenous, common peroneal and tibial nerves. RF neurotomy has been reported to be a reliable method in the management of chronic knee pain related to OA [(9)].

The aim of this study was to compare the pain relieving effect of radiofrequency of genicular nerve versus PRP if injected in the intra-articular osteoarthritic knee joint.

PATIENTS AND METHODS

The present prospective, comparative, randomized study was conducted at Aswan university hospital. Fifty patients with knee osteoarthritis were included. During a 6-month period.

Studied populations were divided into 2 groups: Group I: Which included 25 patients who received a single intraarticular injection of PRP only, and **Group II:** Which included 25 patients who received a single session of radiofrequency ablation of genicular nerves.

Ethical Statement:

The study run was approved by the Aswan University Hospital ethical committee (approval number) and conducted in accordance with the international ethical standards and applicable local regulatory guidelines. A written informed consent was obtained from every eligible patient. All eligible patients signed a written informed consent form after learning the study objectives, methodology, risk, and benefit.

Inclusion criteria: Patients with knee osteoarthritis diagnosed by x-ray or MRI grading having pain for more than 6 months, both sexes included aged above 40 years, pain is not relieved by pharmacological treatment nor physiotherapy, and surgery was rejected by the patient.

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Exclusion criteria: Previous knee surgery, knee sepsis, coagulopathy, patient refusal, and anatomical anomalies.

Randomization process: A computer-generated randomization table has been used for patient allocation to one of the two groups, The PRP group and The RFA group. Patients have been written in a sealed envelope that is only open after patient consents for the study.

All patients were subjected to:

- Patient detailed consent after complete description of the procedure.
- History: full detailed history from the patient will be taken concerning medical treatment, duration of OA and bleeding tendency.
- Thorough examination of the patients and his knee joint regarding range of movement, anatomy and disability.
- Assessment of pain using visual analogue scale (VAS).
- Laboratories: Complete blood count, renal function test, liver function test, and coagulation profile.
- Imaging (X-ray) revision to assess the severity and limitation, also to exclude anatomical anomalies.

Study's Interventions:

I. PRP Group:

Group I received intra-articular injection of 5 ml of PRP then reassessed after 1, 3 and 6 months. PRP was prepared in the same day of injection by collecting 30 ml of the patient blood and send it to the laboratory, giving 5 ml of pure PRP in a sterile container.

II. Radiofrequency Group:

In group II, patients were placed in the supine position and their knee supported by a small pillow placed beneath the popliteal fossa. Fluoroscopic images of tibio femoral joint were obtained.

First, patients are given a diagnostic block under fluoroscopy or ultrasound guidance. Specifically, 1mL of lidocaine is injected using a 20-gauge, 3.5-in (8.9-cm) spinal needle around the superior lateral, superior medial, and inferior medial genicular nerve branches. The diagnostic block is extra-articular. If the patient reports 50% reduction in baseline pain for a minimum of 24 hours following the injection, then the patient is a candidate for genicular ablation **[10].**

Study's Outcomes:

The primary outcome in the present study was to compare the efficacy of PRP and radiofrequency of genicular nerve in reducing the severity of pain as assessed by VAS score after injection, 1 month, 3 month and 6 month. The secondary outcome to assessment of patient satisfaction, which was measured on a 5-point Likert scale (extremely satisfied, satisfied, neutral, dissatisfied, extremely dissatisfied).

Statistical analysis which can use for a Likert scale are:

Summarize using a median or a mode (not a mean as it is ordinal scale data); the mode is probably the most suitable for easy interpretation. Display the distribution of observations in a bar chart (it can't be a histogram, because the data is not continuous) **[11]**.

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Strengths:

Likert Scales have the advantage that they do not expect a simple yes / no answer from the respondent, but rather allow for degrees of opinion, and even no opinion at all. Therefore, quantitative data is obtained, which m means that the data can be analyzed with relative ease. Offering anonymity on self-administered questionnaires should further reduce social pressure, and thus may likewise reduce social desirability bias. **Paulhus** [(12)] found that more desirable personality characteristics were reported when people were asked to write their names, addresses and telephone numbers on their questionnaire than when they told not to put identifying information on the questionnaire[(11)].

Statistical Analysis:

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). The normality of the data were assessed using Shapiro-Wilk Test. Numerical data were described as mean ±SD if normally distributed; or median and interquartile range [IQR] if not normally distributed. Frequency tables with percentages were used for categorical variables. Independent Student t-test and paired t-test were used to compare parametric quantitative variables; while Mann-Whitney tests and Wilcoxon matched pairs test were used to compare non-parametric quantitative variables. Chi-square test or McNemar-Bowker tests were used to analyze categorical variables. Multilinear logistic regression was undertaken to assess the predictors of mortality. A p-value < 0.05 is considered statistically significant.

RESULTS

Studied populations were divided into 2 groups: Group I: Which included 25 patients who received a single intraarticular injection of PRP only. The mean age of the included patients was 53.23 ± 8.03 years and the majority of them were females (80%). The mean BMI was 28.43 ± 2.11 Kg/m^2. **Group II:** Which included 25 patients who received a single session of conventional radiofrequency of genicular nerves. The mean age of the included patients was 56.04 ± 7.58 years and the majority of them were females (76%). The mean BMI was 29.61 ± 1.64 Kg/m^2.

Table (1): The demographic and clinical characteristics of the included patients

Variables	Group I (N =25)	Group II (N =25)	P-value
Age in years			
- Mean ±SD	53.23 ± 8.03	56.04 ± 7.58	(t)p=0.209
- Median (range)	53 (41 - 64)	56 (41 - 62)	
Gender, No. (%)			
- Male	5 (20%)	6 (24%)	(χ^2)p=
- Female	20 (80%)	19 (76%)	0.733
Weight in Kg			
- Mean ±SD	73.36 ± 7.02	76.57 ± 6.58	(t)p=
- Median (range)	73 (61 - 84)	75 (67 - 92)	0.102
Height in cm			
- Mean ±SD	160.57 ± 7.25	160.43 ± 6.57	(t)p=
- Median (range)	160 (149 - 172)	159 (151 - 174)	0.943
BMI in kg/m^2			
- Mean ±SD	28.7 ± 2.11	29.61 ± 1.64	(t)p=
- Median (range)	28 (25 - 32)	29 (26 - 34)	0.095
Duration of OA in years			
- Mean ±SD	3.36 ± 1.02	3.57 ± 1.58	(t)p=

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- Median (range)	3 (1 - 4)	4 (1 - 4)	0.579
Risk Factors for OA, No. (%)			
- Trauma	5 (20%)	6 (24%)	
- Mechanical forces	9 (36%)	8 (32%)	(χ^2)p= 0.928
- Others	11 (44%)	11 (44%)	

There were no statistically significant differences between the included groups in terms of age (p =0.12) and gender (p =0.32) and in terms of weight (p =0.25), height (p =0.504), and BMI (p =0.097), also shows that there were no statistically significant differences between the included groups in terms of duration of OA (p =0.25), and risk factor (p =0.32) (Table 1).

Table (2): The baseline values of the included patients

Variables	Group I (N =25)	Group II (N =25)	(t)P-value
VAS score			
- Mean ±SD	8.25 ± 0.92	8.29 ± 0.80	0.870
- Median (range)	8 (7 - 9)	8 (7 - 9)	

There were no statistically significant differences between the included groups in terms of baseline VAS score (p =0.63) (Table 2).

Table (3): The change in study's outcomes in group I (PRP group):

Variables	Day 0	1 month	3 months	6 months	P-value
VAS score					
- Mean ±SD	8.25 ± 0.9	7.32 ± 0.8	7.8 ± 0.8	8.05 ± 0.8	0.28
Patient satisfaction					
Very satisfied	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	
Slightly satisfied	0(0.0%)	1(4.0%)	1(4.0%)	2(8.0%)	
Neutral	1(4.0%)	4(16.0%)	5(20.0%)	5(20.0%)	0.610
Slightly dissatisfied	3(12.0%)	4(16.0%)	4(16.0%)	4(16.0%)	
Very dissatisfied	21(84.0%)	16(64.0%)	15(60.0%)	14(56.0%)	

The PRP did not significantly improve the VAS score (p =0.28) (Table 3).

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Table (4): The change in study's outcomes in group II (Radiofrequency group)

Variables	Day 0	1 month	3 months	6 months	P-value
VAS score					
- Mean ±SD	8.25 ± 0.9	2.89 ± 0.8	4.46 ± 0.8	4.46 ± 0.8	<0.001*
Patient satisfaction					
Very satisfied	0(0.0%)	1(4.0%)	13(52.0%)	15 (60.0%)	
Slightly satisfied	2(8.0%)	4(16.0%)	5(20.0%)	8 (32.0%)	
Neutral	1(4.0%)	5(20.0%)	7(28.0%)	2 (8.0%)	<0.001*
Slightly dissatisfied	3(12.0%)	6(24.0%)	0(0.0%)	0 (0.0%)	
Very dissatisfied	19(76.0%)	9(36.0%)	0(0.0%)	0 (0.0%)	

*: Statistically significant at $p \leq 0.05$

The radiofrequency of genicular nerve significantly improved the VAS score (p =0.001) (Table 4).

Table (5): The outcome of the included patients at the end of follow-up

Variables	Group I (N =25)	Group II (N =25)	P-value
VAS score			
- Mean ±SD	8.05 ± 0.8	4.46 ± 0.8	<0.001*
Patient satisfaction			
Very satisfied	8 (32.0%)	0(0.0%)	
Slightly satisfied	6 (24.0%)	2(8.0%)	
Neutral	4 (16.0%)	5(20.0%)	0.002*
Slightly dissatisfied	3 (12.0%)	4(16.0%)	
Very dissatisfied	4 (16.0%)	14(56.0%)	

*: Statistically significant at $p \leq 0.05$

There were statistically significant differences between the included groups in terms of VAS score (p =0.63), at the end of follow-up. The radiofrequency of genicular nerve group showed statistically significant lower values than the PRP alone group (Table 5).

DISCUSSION

In Group I the mean age of the included patients was 53.23 ± 8.03 years and the majority of them were females (80%). The mean BMI was 28.43 ± 2.11 Kg/m^2. **In Group II** the mean age of the included patients was 56.04 ± 7.58 years and the majority of them were females (76%). The mean BMI was 29.61 ± 1.64 Kg/m^2.

In line with our findings, **Eberly and colleagues** [13] examined the possible relation between knee-pain scores and several psychosocial, sociodemographic, disease, and treatment variables in 355 patients with knee OA. the patients ranged in age from twenty-four to ninety years. The average BMI was 31.0 kg/m^2 (range, 19.1–61.9 kg/m^2). in addition, the majority of patients were females.

Likewise, **Burgos-Vargas and colleagues** [14] aimed to determine the demographic, clinical, and therapeutic characteristics of patients with OA in Argentina, Brazil, and Mexico. In all, 1210

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patients (mean age [±SD]: 61.8 [12.0] years) with knee OA were included in the study; 978 (80.8%) were females and 232 (19.2%) males, with a mean age of 59 years old.

Regarding the effect of PRP on study outcomes, we found that PRP did not significantly improve the VAS score (p =0.28).

In contrary to out findings **Chung et al.** [15]. performed a meta-analysis looking at 14 randomized clinical trials (RCTs), comprising of 1423 patients, comparing PRP to various controls including placebo, hyaluronic acid, corticosteroid injections, oral medications, and homeopathic treatments. The meta-analysis showed a significant improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at 3-, 6-, and 12-month follow-up (= 0.02, 0.04, < 0.001 respectively). Subgroup analyses examining the efficacy of PRP based on severity of knee OA have shown PRP to be more effective in patients with mild to moderate OA. Authors have suggested that intra-articular PRP injections are more efficacious in the treatment of knee OA, in terms of pain relief and patient-reported outcomes, than other alternative injections.

The difference between our findings and the above mentioned studies can be explained by the difference in population's characteristics. It was reported that the characteristics of knee OA varies significantly by geographical region. In addition, the high severity of knee OA in our cohort might have played an additional role to this findings.

Regarding the effect of radiofrequency of genicular nerve on study outcomes, we found that radiofrequency of genicular nerve significantly improved the VAS score.

In concordance with our findings, RFA was first compared to intra-articular injections in the 2016 **Sarı et al**. [10] trial. Seventy-three patients with at least grade 2 Kellgren–Lawrence OA were randomized to receive either RFA of the SL, SM, and IM genicular nerves at 80°C for 90 seconds or intra-articular injection of bupivacaine, morphine, and betamethasone. Patients were assessed at baseline, 1 and 3 months for pain level via VAS and function via the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index. Results showed statistically superior pain relief with RFA at 1 and 3 months, but superiority in the total WOMAC score with RFA only at 1 month. Limitations of the study include the lack of prognostic blocks, the unrestricted and undocumented use of oral analgesics, and the lack of a true control group.

The SM, IM, and SL genicular nerves were also targeted in the 2017 **Qudsi-Sinclair et al.** [16] trial, but in this trial the effect of RFA was examined only in patients with a history of total knee arthroplasty (TKA). Thirty patients with refractory knee pain that persisted at least 6 months following TKA were enrolled in the study, with 28 completing follow-up to 12 months. Patients were randomized to receive either continuous RFA at 80°C or sham RFA that consisted of genicular nerve blocks with local anesthetic and corticosteroid. Both procedures were performed under fluoroscopic guidance. Outcome measures were pain level assessed via a numeric rating scale (NRS), and function assessed via both the OKS and Knee Society Score. Outcomes with respect to function were modest and similar between groups, with most improvements occurring between months 1 and 6, and declining toward baseline by 12 months. Pain also decreased in both groups, but the reduction following RFA peaked at 3 months and persisted at 12 months, while the control group experienced their lowest NRS on day 1 and then steadily increased toward baseline at 12 months. This trial is limited by a small size and the lack of prognostic blocks pre-RFA, which may have led to the inclusion of nonresponders in the RFA group.

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The **Chen et al.**[17] trial compared RFA with PRP and sodium hyaluronate (HA) to PRP and HA alone. Inclusion criteria were refractory pain of at least 3 months duration due to OA and pain level of at least 6 on a 0–10 VAS. Both groups received intra-articular injections of PRP and HA weekly for 5 weeks, but the treatment group also received RFA at 70°C, although the timing of the RFA was not described. The precise nerves were also neither named, nor was it specified whether image guidance was used. Twenty-seven patients were randomized to each group and follow-up was obtained at the completion of intra-articular injections and 3 months. Outcome measures included pain intensity as measured on a VAS, life quality as measured on the 36-item Short-Form Health Survey, and function via the American Knee Society Score. Both groups showed improvement in pain and function, although the gains in the RFA group were statistically superior at all time periods. The RFA group also demonstrated significant improvement in quality of life at 3 months, while the control group did not.

The 2018 trial by **Davis et al**. [18] is the largest study and was also the first to employ CRFA. Similar to the **Choi et al.** [9] **and Qudsi-Sinclair et al.** [16]**,** the SM, SL, and IM genicular nerves were targeted. Inclusion criteria were the presence of at least grade 2 Kellgren–Lawrence radiographic OA, refractory knee pain of at least 6 month duration, pain of at least 6 of 10 on a NRS, OKS score of at least 35, and at least 50% improvement with genicular nerve blocks. One hundred and fifty-one patients met the inclusion criteria and were randomized to receive either CRFA or intra-articular steroid (IAS) injection. CRFA was performed under fluoroscopic guidance with 17-gage introducers at 60°C for 150 seconds. The primary outcome was the percentage of patients achieving at least 50% pain reduction at 6 month follow-up as measured by a NRS. Secondary outcome measures included function measured on OKS, patient's overall perception of the treatment, and analgesic usage. Pain relief with CRFA was superior to that obtained with IAS at all time periods, and at 6 month follow- up 74% of the CRFA group had at least 50% relief compared to just 16% of the IAS group. Function and global perception were also superior in the CRFA cohort, although there was no statistical difference between the groups in terms of oral opioid use. The longer duration of relief noted in this study provides evidence for the theoretical benefit of CRFA, namely the creation of larger lesions to reduce the technical failure rate (i.e., missed nerves) .

The most recent RCT by **El-Hakeim et al.** [19] compared RFA to non-interventional therapy. Sixty patients with at least grade 3 Kellgren–Lawrence OA were randomized to receive either RFA of the SM, SL, and IM branches or conventional treatment with oral acetaminophen and diclofenac. RFA was accomplished with three 90 seconds cycles at 90°C per site, which is a substantially longer duration of RFA than that employed by any other RCT. Patients were evaluated at baseline, 2 weeks, 3 months, and 6 months. Results showed statistically superior pain relief with RFA at all follow-up intervals. Function as assessed by the WOMAC index was improved in both groups at 6 months, but was superior with RFA. Lastly, patient satisfaction as measured on a Likert scale was significantly higher at 3 and 6 month follow-up in the RFA group. However, the study is limited by the lack of pre-RFA prognostic blocks and the lack of patient blinding.

In terms of comparison analysis, we found that there were statistically significant differences between the included groups in terms of VAS score ($p = 0.63$), at the end of follow-up. The radiofrequency of genicular nerve group and showed statistically significant lower values than the PRP alone group.

Study's Limitations: We acknowledge that the present study has some limitations. the study was limited to Aswan University hospital only and therefore the results cannot be generalized to the general Egyptian population.

Recommendation of the authors: Radiofrequency of genicular nerve is an effective modality in reducing the pain and improving the mobility of the knee in patients with knee osteoarthritis in patients who are no responder to pharmacological treatment. Therefore, it recommended to include radiofrequency of genicular nerve in this population group.

CONCLUSION

In conclusion, our analysis showed that, for short-term follow-up (≤ 1 year), radiofrequency of genicular nerve is an effective modality in reducing the pain and improving the mobility of the knee in patients with knee osteoarthritis in patients who are no responder to pharmacological treatment. On the other hand, single injection of intra-articular PRP injection is not effective in the same population group. A randomized controlled trial with larger group sizes is necessary to find the predictors of the response to PRP. Nevertheless, further studies with rigorous design, large sample size and multiregional cooperation are required.

RECOMMENDATIONS

Radiofrequency of genicular nerve is an effective modality in reducing the pain and improving the mobility of the knee in patients with knee osteoarthritis in patients who are no responder to pharmacological treatment.

Therefore, it recommended to include radiofrequency of genicular nerve in this population group. Nevertheless, further studies with rigorous design, large sample size and multiregional cooperation are required.

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