



COMPARISON OF EFFICACY OF INTRA ARTICULAR INJECTION WITH PLATELET-RICH PLASMA, HIGH MOLECULAR WEIGHT HYALURONIC ACID AND METHYLPREDNISOLONE IN OSTEOARTHRITIS OF KNEE.

Physical Medicine

S. Pati	Department of Physical Medicine and Rehabilitation, IPGME&R and SSKM, Hospital, Kolkata, India.
R. Pramanik	Department of Physical Medicine and Rehabilitation, IPGME&R and SSKM, Hospital, Kolkata, India.
J. Panda	Department of Onco- Pathology, Hope and Heal Cancer Center, Siliguri, West Bengal India.
P.P.Pan	Department of Physical Medicine and Rehabilitation, NBMCH, Siliguri, West Bengal, India

ABSTRACT

Background: In treatment of osteoarthritis of knee intraarticular steroid is an age-old low-cost weapon and Hyaluronic acid injection is a costlier alternative. The study was done to compare efficacy of Platelet rich plasma in relieving pain and improving functional outcome and whether it can be an alternative to both. **Methods:** 120 patients were divided into 3 groups (40 each) and injected with methyl prednisolone (steroids) (Group A), Hyaluronic Acid (HA) (Group B) and Platelet Rich Plasma (PRP) (Group C) and followed at 6 weeks and 12 weeks to evaluate improvement in Pain (VAS), WOMAC score and 50 feet walking speed (functional outcome). **Results:** Changes in VAS at Pre-injection (VAS0) and at 6 weeks (VAS6) in Group A (Mean diff 3.8750, 95% CI of diff 3.2448 to 4.5052) showed more improvement than Group B and Group C, (Mean diff 2.7250, 95% CI of diff 2.1413 to 3.3087). VAS0 when compared with VAS12 showed improvement throughout, with improvement more in Group B and C (Mean diff 4.3000, 95% CI of diff 3.7163 to 4.8837) than Group A (Mean diff 2.7500, 95% CI of diff 2.1198 to 3.3802). VAS6 vs VAS12 showed a dip in improvement in Group A (Mean diff -1.1250, 95% CI of diff -1.7552 to -0.49477) whereas Group B and C showed continuous improvement pattern (Mean diff 9.1365, 95% CI of diff 0.99128 to 2.1587). Similar results are seen in WOMAC and 50 feet walking speed. **Conclusion:** Improvement was seen in all groups with HA and PRP showing better improvement in long-term.

KEYWORDS

INTRODUCTION

Osteoarthritis (OA) of knee is a very common, relatively benign but seriously disabling condition which physiatrists must attend on day-to-day basis in their hospitals. According to WHO, OA is the second most commonest musculoskeletal problem in the world population (30%) after back pain (50%) (Anthony D. Woolf and Bruce Pfleger, 2003). Even one of the latest molecules, high molecular weight hyaluronic acid (HA), failed to show significant disease modification in osteoarthritis of knee in the last decade. According to OARSI 2014 guidelines its recommendation is "Uncertain" in knee-only OA and "Not appropriate" in multiple-joint OA with quality of evidence as "good" (T E McAlindon et al., 2014).

Platelet Rich Plasma (PRP) is one of the newer weapons added in Physiatrists armamentarium recently. Most of the molecules which proved to be beneficial for symptomatic relief in osteoarthritis knee, failed to modify the disease process and regenerate cartilage whereas PRP as per literature has the potential, theoretically to revert the destruction process in osteoarthritis of knee (Anitua E et al., 2004). Although there are a few evidences in literature claiming the role of cartilage regeneration by high molecular weight hyaluronic acid (Gene A Homandberg et al., 2003).

Methyl prednisolone is an age-old, low-cost and an excellent option for symptomatic relief in osteoarthritis knee and in reduction of flare-ups of the disease but debate exists regarding long-term effects and disease modification. As per OARSI 2014 guidelines recommendation, it is "Appropriate" in knee-only OA with quality of evidence as "good" (T E McAlindon et al., 2014). Intra articular steroids can cause certain disabling side effects like avascular necrosis (PI Kontovazenitis et al., 2009)

Hence this is our sincere effort to compare the efficacy of platelet-rich plasma, high molecular weight hyaluronic acid and methyl-prednisolone and to find out if PRP can replace the intra-articular steroid and costlier hyaluronic acid.

METHODS

Institutional ethics committee clearance was taken from the Ethics Committee of IPGME&R and SSKM Hospital for this study (Memo No. Inst/IEC/2015/092)

Study Area And Sampling Strategy

The study was done in the Department of Physical Medicine and Rehabilitation, IPGME&R and SSKM Hospital, Kolkata on patients with primary OA Knee who attended the outdoor clinic. Individual informed consent was taken from the patients who wished to be included in this study. Sample size for the study was calculated on the basis of VAS pain score as the primary outcome measure. It is calculated that 40 subjects will be required per group in order to dictate the difference of 10mm in VAS pain score between the two groups with 80% power and 5% probability of Type I error. This calculation assumes a standard deviation of 15mm of VAS pain score and two-sided testing. Sample size calculation was done by using nMASTER 2.0 software (Department of Biostatistics, Christian Medical College Vellore).

The sampling strategy was done with all the patients attending PMR OPD who fell under inclusion criteria and were willing to participate in the study. Randomization was done using computer generated registration number given to the patients where numbers ending with 1,4,8 was taken in steroid group, numbers ending with 0,3,7 in HA group and numbers ending with 2,5,9 in PRP group.

Inclusion And Exclusion Criteria

Confirmed cases of grade II and III osteoarthritis knee as per Kellgren and Lawrence classification with VAS greater than or equal to 5 were included in the study and Grade IV and I as well as patients with contraindication to steroid, high molecular weight hyaluronic acid and platelet rich plasma were excluded. Patients with thrombocytopenia, secondary OA knee, anemia, systemic disease, hematologic disease, history of tumor or active tumor, severe cardiovascular disease, infection, immunosuppressive status, and application of intra-articular depot glucocorticoid injection or HA within 3 months before application of tested substance were also excluded from the study.

Study Parameters

- 1) Visual analog scale (VAS) was used to evaluate pain.
- 2) The Western Ontario and McMaster Universities (WOMAC) Scale was used to study functional outcomes.
- 3) 50 feet walk time (in seconds) was also used as a functional outcome measure.

Study Techniques

In this study patients suffering from primary osteoarthritis of the knee have been selected for intervention according to inclusion and

exclusion criteria. The selected patients were explained in details about the disease and study intended to be done. Prior to intervention base line VAS and WOMAC score and 50 feet walking speed were noted in the following manner. A 10 cm horizontal visual analogue scale (VAS) was used for pain measurement, with 0 being no pain and 10 being the worst pain in patient's life. For fifty feet walking time patient was asked to walk a distance of 50 feet in bare feet in a plane surface without obstacle with maximum speed which was comfortable to the patient and the time was recorded with a standard stop watch in seconds. WOMAC score was noted in a chart. The selected patients were divided into three groups (A, B and C) randomly. Patients in Group A received 2ml (40mg/ml) intra-articular injection of methylprednisolone (steroid) mixed with 1 ml of 2% lignocaine. Patients of Group B received 6ml of intra-articular injection of high molecular weight hyaluronic acid (HA), and Group C patients received 6ml of freshly prepared intra-articular injection of Platelet Rich Plasma (PRP) in the involved knee joint. The injections were administered under strict aseptic condition. Before injecting any drug, aspiration was attempted under aseptic condition and fluid was aspirated as much as possible. All injections were administered based on landmark technique and by a single person. After administering injections, the patients assessed at the interval of 6 weeks (1st Visit) and 12 weeks (2nd visit) using the parameters mentioned above. The results have been analysed according to the standard statistical methods to fulfil the aims and objectives of the study. All patients were educated regarding joint protection techniques and lifestyle modification. They were also demonstrated and advised to perform range of motion exercises of knee and quadriceps strengthening exercises. Only paracetamol 1 g was advised as analgesic on SOS basis with a maximum tablet of two a day

Result Analysis

Data was summarized by routine descriptive statistics, such as mean and standard deviation for numerical variable, when normally distributed or median or interquartile range when skewed. Counts and percentages were used to categorize the variable. Numerical variables were compared between groups by One-way Analysis of Variance (ANOVA), when normally distributed, followed by appropriate post hoc multiple comparison test.

Chi-Square test was employed for comparing independent proportion between groups. $P < 0.05$ was considered statistically significant and all analysis was two tailed

Software Used were Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] and GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007]

RESULTS

Patient Related Information

Sex Ratio In Each Group

There were total of 40 patients in each group. With 26 males and 14 females in Group A, 23 males and 17 females in Group B, 22 males and 18 females in the Group C

Grade Of OA In Each Group

Group A had 23 patients with grade II OA Knee and 17 with Grade III, Group B had 18 patients and 22 patients in Grade II and Grade III OA knee respectively with Group C having 19 and 21 patients in grade II and grade III OA Knee

Involvement Of Knee

In Group A, 25 patients had right knee involvement whereas in 15 patients left knee was involved. In Group B there were 21 patients of right-sided knee pain and 19 of left sided knee pain. Group C had 22 and 18 patients with right and left knee involved respectively.

Age Of Patients

The average of patients we got in Group A was 51.65 years, Group B was 48.12 years and Group C was 47.87 years.

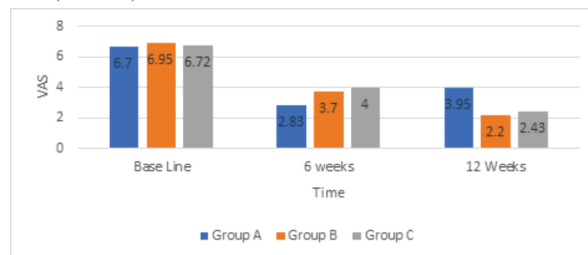
Analysis

Data was analysed by One-way Analysis of Variance (ANOVA), Chi-square tests as mentioned above. The Turkey's Multiple Comparison Test was used to compare and analyse the intra group data.

VAS Comparison

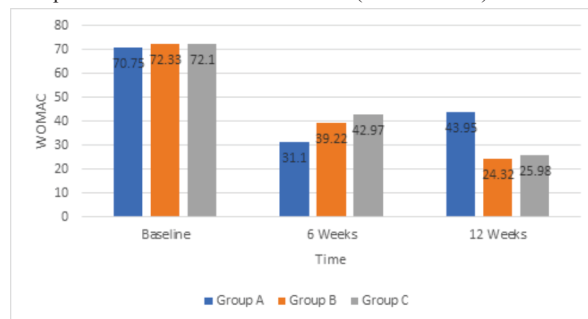
As Depicted below the VAS or the Pain intensity on comparison at 6 weeks showed maximum decrease in Group A (6.7 to 3.7) followed by

Group B (6.95 to 3.7) and Group C (6.72 to 4). At 12 weeks Group A Shows increase in VAS than at 6 weeks (2.83 to 3.95), Group B has further decrease in VAS (3.7 to 2.2) and Group C too shows decrease in VAS (4 to 2.43).



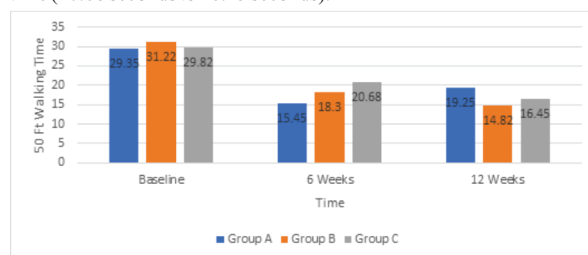
WOMAC Comparison

The WOMAC or the functional improvement on comparison at 6 weeks showed maximum improvement in Group A (70.75 to 31.1) followed by Group B (72.33 to 39.22) and Group C (72.1 to 42.97). At 12 weeks Group A shows increase in WOMAC than at 6 weeks (31.1 to 43.95), Group B has further decrease in WOMAC (39.22 to 24.32) and Group C too shows decrease in WOMAC (42.97 to 25.98).



50 Feet Walking Time Comparison

The 50 feet walking time on comparison at 6 weeks had maximum improvement in Group A (29.35 seconds to 15.45 seconds) followed by Group B (31.22 seconds to 18.3 seconds) and Group C (29.82 seconds to 20.68 seconds). At 12 weeks Group A showed increase in 50 feet walking time than at 6 weeks (15.45 seconds to 19.25 seconds), Group B has further decrease in 50 feet walking time (18.3 seconds to 14.82 seconds) and Group C too shows decrease in 50 feet walking time (20.68 seconds to 16.45 seconds).



DISCUSSION

This study was conducted over a period of 18 months from mid-January 2015 to mid-July 2016 after taking permission from institutional ethics committee in Department of Physical Medicine and Rehabilitation IPGMR and SSKM Hospital with objectives to see efficacy of Platelet Rich Plasma, High molecular weight Hyaluronic Acid and Methyl prednisolone in treatment of OA knee and to compare the efficacy between them in patients with Grade I and Grade II OA knee. Most of our patients were from rural area. (Ajit and Nisha, 2014) pointed out more prevalence of the disease in rural than urban areas probably due to the difference in lifestyle but it was beyond the scope of our study to compare the prevalence of disease among different socio-economic status and living conditions.

Mostly our patients were middle aged with average age of 49.2 years and we got male preponderances with 60.67% of patients being male and 39.33 % being females. (Martin JA and Buckwalter JA, 2002) points out that age is an important risk factors with maximum prevalence of the disease is seen above 75 years and (MC Nevitt and D T Felson, 1996) points out the fact that women are more likely than male in getting OA. On the contrary (Martin JA, Buckwalter JA, 2002) showed that prevalence is almost same in men and pre-menopausal

women. The objectives of the study did not include seeing the prevalence of the disease as the sample size was small.

As per (Marco Paoloni et al., 2015) there is limited role of intervention in radiological Grade I OA knee, which is best managed by conservative means. And GIV OA knee generally requires total knee replacements, hence we avoided taking these grades of patients in our study populations.

We had 23 patients with KL Grade II OA knee and 17 with KL Grade III OA knee in steroid group with HA group having 18 and 22 patients respectively in each group and PRP group has 19 and 21 patients in KL Grade I and KL Grade II OA knee. One of the limitations of our study is that we did not compare the efficacy of steroid PRP or HA according to the grades of OA knee. (Tímea Spaková et al., 2012) points out that PRP has better effect in early OA knee.

In our study we got statistically significant improvement with respect to reduction in VAS, improvement in WOMAC and 50 feet walking time in all the three groups.

It is seen that VAS for joint pain at 6th week (1st follow up) there is 57.76% of pain reduction compared to pre injection state in steroid group followed by 46.76% in HA group and 40.76% in PRP group. But in 2nd visit (i.e. at 12th week) there is 39.57% of increase in pain compared to 1st visit in steroid group with both HA (40.45%) and PRP (39.25%) showing sustained pain reduction. In long term comparison (i.e. from 0 week to 12 weeks), there is 41.04 % of pain reduction with steroid, 63.83% by PRP and HA shows the maximum reduction of 68.34% Almost similar kind of results were seen by (N Bellamy et al., 2006) for intra articular injection with methyl prednisolone. The study did not include PRP unlike us.

Similarly, on analyzing WOMAC score in the 1st follow up visit at 6 weeks, steroid has 55.92% improvement, HA has 45.47% and PRP has 40.38% showing steroid is much more effective in initial part but at 2nd follow up of 12th week post injection the improvement in steroid group dips by 41.32% from previous follow up at 6th week. HA and PRP maintains at 37.99% and 39.54% respectively and in long term follow up steroid maintains improvement by 37.70%, HA by 66.37% and PRP by 63.96% which shows that both HA and PRP are better in long term effects. Similar findings are also seen in improvement of 50 feet walking time as shown in result analysis section with long term improvement of steroid being 34% HA being 52.55% and PRP being 44.83%.

A meta-analysis by (Bruce Arroll, and Felicity Goodyear-Smith, 2004) on the efficacy of IA corticosteroids for knee OA showed benefit that lasted for only 2 weeks where as in our study we got effects upto 12 weeks (further follow up was not done) with maximum effect up to 6 weeks only. Additional data from the meta-analysis suggested that high corticosteroid doses (i.e., doses of 50 mg equivalent of prednisone) may be required to achieve a longer response but since we used 40 mg of methyl prednisolone hence effects of higher dose could not be compared.

(Giannini S et al., 2008) published a study of 46 patients showing benefit of PRP in reducing pain and improving quality of life in low grades of OA knee. We too got similar results with limitation of our study being grades of OA and effects not being compared in any of the group.

(M Sánchez et al., 2008) published a study on the effectiveness of intra-articular injections of PRP with 30 patients being treated with PRP and 30 patients treated with HA. They suggested that knee OA treated with the application of PRP could present new and safe possibilities for enhanced outcomes. We also found similar results of HA and PRP both giving very good long-term effects of 12 weeks, showing the possibility of PRP giving a new dimension in treating OA Knee with the advantage of PRP being much less costly than HA.

(Tímea Spaková et al., 2012) compared effects of PRP and HA in 120 patients with one group of patients (60 joints) received PRP and the other group (60 joints) received HA. WOMAC and Pain Numeric Rating Scale scores improved in both PRP and HA groups at 3 months, with slight worsening at 6 months but it remained statistically better than before treatment. The PRP group had statistically superior outcomes. We found in our study that HA group was slight better than

PRP group in all the outcomes with both being more effective than pre-treatment period. Similar to the study we used inactivated PRP.

PRP is prepared from autologous blood, so adverse effects like allergic reactions or transfer of diseases are eliminated (Steven Sampson et al., 2008). PRP also do not promote hyperplasia, carcinogenesis, or any tumour growth though there is possibility of temporary worsening of symptoms after application of PRP. We documented mild worsening of knee pain after injections of PRP in two cases. The pain disappeared spontaneously in all cases within 2 days.

The reasons of PRP acting for longer duration along with HA whereas steroid acted for short term period as seen in our study and few more studies mentioned above are beyond the scope of this study but possible explanation may be based on mechanism of action as steroid reduces pain by its anti-inflammatory properties but fails to prevent disease progression where as both HA and PRP acts according to studies by halting disease progression and in case of PRP it promotes release of various growth factors with time which prolongs its action as well as causes stem cell proliferation (Egemen Ayhan et al, 2014)

Our study like other studies had limitations like relatively small sample size, frequent follow ups could not be done and needed further long-term follow-ups. The effects of treatment on different stage of OA are also not seen but the clinical results are encouraging to further extend the study with longer follow ups and opens up scopes for further studies with PRP with different modes of preparation and their effects as well as combining PRP and visco supplementations to see if there are any synergistic effects. Successful clinical trials on PRP will increase new perspectives on treatment of degenerative joint disease.

CONCLUSION

Statistically significant ($p < 0.001$) improvement pattern is seen due to intraarticular injection of steroid, high molecular weight hyaluronic acid and platelet rich plasma throughout the study period.

Intra group comparison showed that, the maximum improvement at end of 12 weeks is seen due intervention with Hyaluronic acid (68.34% in VAS, 66.37% in WOMAC and 52.55% in 50 feet walking time) closely followed by Platelet Rich Plasma (63.83% in VAS, 63.96% in WOMAC and 44.83% in 50 feet walking time)

There is statistically significant improvement with intra articular injection of Methyl prednisolone upto 12 weeks, the improvement pattern of VAS, WOMAC and 50 feet walking time decreased in the latter half of the study (i.e. from 6 weeks to 12 weeks).

So, we can conclude that in short duration intra articular injection with steroid is superior but in long duration HA and PRP with HA being slight superior to PRP is better in relieving symptoms of OA Knee and improving functional outcome.

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