

ORIGINAL ARTICLE

Duloxetine in Addition with Platelet Rich Plasma in Managing Neuropathic Knee Pain: A Comparative Study

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Abstract

Background: Osteoarthritis of knee joint is one of the most prevalent forms of arthritis in the world. With the progressive ageing of the population, it becomes a major public health concern. Knee osteoarthritis with neuropathic pain further increase the sufferings resulting functional limitation. Various conservative and intra-articular therapies have been used but none proved to be ideal for the treatment of chronic osteoarthritis. Current research in investigating new methods for stimulating repair or replacing damaged cartilage by using biological agents like platelet rich plasma in chronic osteoarthritis. Combination of platelet rich plasma therapy along with orally given duloxetine can provide better outcome for neuropathic pain and functional limitation.

Methods: This study was carried out in the Pain Clinic, Department of Anaesthesia, Analgesia and Intensive Care Medicine, BSMMU during the period of May 2019 to April 2020. The patients were randomly assigned to one of the two groups (group A= only intra articular PRP; group B= PRP with oral Duloxetine 20mg) using a computer generated random sampling. After providing the allocated treatment, all patients were undergone follow-up examination at 1st week, 1st month and 3rd month after the procedure by International Knee Documentation Committee (IKDC) score, DN4 questionnaire and VAS scale. Pain intensity and neuropathic pain status were assessed by visual analog scale (VAS) and DN4 questionnaire. Whereas IKDC score was used to assess functional impairment of affected knee joint. Follow up were carried out by visiting in Pain Clinic at mentioned intervals or over phone. The significance of the difference of the DN4 score, visual analogue scale (VAS) and International Knee Documentation Committee (IKDC) score at 1st week, 1st month, and 3rd month were tested by using unpaired t- test, chi-square test and fisher exact test.

Results: To assess functional improvement of affected knee joint, group B mean IKDC score was more than Group A in all follow up period, but statistically significant results were observed in 1st month (50.92±3.85) and 3rd month (55.54±4.64) follow up. Mean DN4 score and VAS score at pretreatment and 1st week were not statistically significant between the groups. But at 1st month and 3rd month both DN4 score and VAS score showed statistically significant difference between the groups. Inter group comparison showed that, mean DN4 score in group B (2.45±0.59) grossly decreased than group A (5.20±0.51) which indicate statistically significant reduction of neuropathic pain between the groups. Group B mean VAS (2.15±0.36) score decreased more than Group A (4.75±0.43) showed statistically significant improvement of pain in group B than group A.

Conclusion: Intra articular platelet rich plasma in combination with oral duloxetine provide better pain relief and improvement of functional status than PRP alone in chronic knee osteoarthritis with neuropathic pain.

Keywords: Osteoarthritis, Knee pain, Neuropathic pain, PRP, Duloxetine, VAS, DN4, IKDC

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Introduction

Disability has a substantial impact on the quality of life of patients and affects daily living¹. It is associated with extensive direct and indirect costs and represents a considerable burden for the health care system and the society in general. Pain influences functional disability of patients suffering from OA². Osteoarthritis is a chronic joint disease characterized by progressive destruction of articular cartilage, thinning and eventually wearing of articular cartilage. The degeneration of articular cartilage, mainly due to changes in the activity of chondrocytes in favour of catabolic activity which also involves other joint tissues, as alternations of the meniscus, sclerosis and oedema in the underlying subchondral bone as well as intermittent inflammation of synovium. This condition impairs functional capacity and decrease quality of life (QoL) in patients by producing pain, stiffness and limitation in range of motion of the joint³.

Osteoarthritis (OA) is the most prevalent of the chronic degenerative diseases and is a leading cause of pain and disability in most countries worldwide⁴. The prevalence of OA increases with age and generally affects women more frequently than men⁵ and about 12.1% of the population from 25 to 74 years of age suffering from knee OA. Community-based studies have shown that of the population over the age of 55 has troublesome knee pain, and many of them are severely disabled⁶. According to community- oriented programme for control of rheumatic diseases (COPCORD) studies conducted in Pakistan in 1998, 3.7% of the 209 subjects were found to be suffering from knee OA⁷. Features of OA include progressive cartilage degradation, subchondral bone remodelling, synovitis, and chronic pain. So, it is the leading cause of physical disability in people. In Bangladesh, it is reported that people suffered from osteoarthritis about 10.20%⁸.

Knee OA has been characterized as an insidious disease related to structural changes in the joint over many years and decades. Progressive and irreversible articular damage results in a loss of the extracellular matrix of cartilage in addition to changes in subchondral bone. These degenerative changes result

in cartilage loss, synovitis, subchondral cysts, bone marrow lesions, and osteophyte formation. It is also characterized by an attempt of the joint to regenerate tissue such as fibrocartilage⁹. Some studies have directly evaluated the presence of articular somatosensory lesions. Samples obtained during knee replacement surgery of patients with OA indicate that, compared with healthy joints, there is an infiltration of immune cells, increased angiogenesis and increased growth factor expression in osteochondral junctions. These alterations possibly contribute to the sympathetic and sensory neurovascular infiltration into what is, in healthy individuals, a minimally innervated and avascular structure. This ectopic innervation seemed to arise from the subchondral bone¹⁰. In a similar study, osteochondral junction samples from patients with OA had higher vascularization and expression of the neuropeptide calcitonin gene-related peptide (CGRP) than in healthy patients¹¹.

Individuals with knee OA with joint-pain co-morbidities are more fatigued, experience lower quality of life, more bodily pain, deprived functioning, and might even be at risk for depressive symptoms compared with people without joint-pain comorbidities¹². Pain intensity, educational level, BMI and social contacts are the most important factors associated with disability of the lower limb in patients suffering from osteoarthritis of the knee or hip². Osteoarthritis of the knee causes pain, limits activity, and impairs quality of life¹³. So, people with osteoarthritis of the knee have neuropathic pain symptoms (shooting or burning pain, pins and needles), the role of centrally active agents, including selective serotonin and noradrenaline reuptake inhibitors has been of interest. At this stage, duloxetine is the only agent to have been examined in a high quality Randomized Controlled Trial (RCT)¹⁴.

Knee OA pain is similar to chronic pain, results in changes in the CNS, which likely reflect alterations in supraspinal modulation of nociception, and increases in excitatory and decreases in inhibitory modulation pathways¹⁵. Duloxetine is serotonin–norepinephrine reuptake inhibitor is used to treat major depressive disorder, generalized anxiety disorder, fibromyalgia, and neuropathic pain. It potentiates 5-HT and NE activity

in the CNS results in pain inhibition¹⁶. Duloxetine increases dopamine (DA) specifically in the prefrontal cortex, where there are few DA reuptake pumps, via the inhibition of Norepinephrine (NE) reuptake pumps, which is believed to mediate reuptake of DA and NE. Duloxetine has no significant affinity for dopaminergic, cholinergic, histaminergic, opioid, glutamate, and GABA reuptake transporters, however, and can therefore be considered to be a selective reuptake inhibitor at the 5-HT (Hydroxytryptamine) and NE (Norepinephrine) transporters¹⁷.

For the knee OA, various conservative treatment modalities are recommended by clinical guidelines¹⁸. The non-pharmacological modalities are patient education and self-management, exercises, weight reduction, walking supports (crutches), bracing, shoe and insoles modification, local cooling/heating, acupuncture, and electromagnetic therapy. Pharmacologic therapies can be summarized as paracetamol, non-steroidal anti-inflammatory drugs, opioids, and slow-acting drugs (glucosamine and chondroitin sulfate). If orally administered drugs are ineffective, intraarticular (IA) injection (corticosteroids, viscosupplements, blood-derived products) is the last nonoperative modality that can be preferred¹⁹.

Although there are several modalities of treatment present for Knee OA, among them Pharmacological agents, knee debridement, osteotomy, and knee replacement surgeries are used for treatment of OA. Non-steroidal anti-inflammatory drugs, opioids, and disease modifying agents have been used since long for symptomatic relief in OA but all of these drugs are associated with adverse effects. Recently, platelet rich plasma (PRP) is a new advancement in treatment of OA. From 1970, various studies were performed on different platelet concentrations in plasma. This was followed by work on the higher amounts of growth factors present in platelets and from those years the first clinical applications of platelet rich plasma (PRP) were investigated. Classically, PRP is considered as a volume of plasma containing higher concentrations of platelets compared to blood base line level²⁰.

Combined platelet rich plasma therapy and duloxetine per oral in knee OA improve lubrication, healing of

soft tissue, regeneration of joint and reduce neuropathic pain associated with knee OA. In doing so, these minimal invasive treatment not only aim to reduce clinical symptoms but also interfere with OA progression. The purpose of the present study is to assess the functional improvement and reducing neuropathic pain after giving of combined PRP with oral duloxetine therapy compared with traditional PRP alone.

Methods

Study place, participants and design

This single blind randomized controlled trial was carried out in the Department of Anaesthesia, Analgesia and Intensive Care Medicine, BSMMU, Dhaka from May 2019 to April 2020. All adult patients aging 40-60 years with grade I and II knee osteoarthritis (Kellgren and Lawrence grading) attending the Pain Clinic Outdoor, Department of Anaesthesia, Analgesia and Intensive Care Medicine were included. Patients with haematological disorder, immunodeficiency, immunosuppression, rheumatoid or polyarticular arthritis, total or subtotal meniscectomy (2/3 excised), treatment with corticosteroids (< 3 months), and on anticoagulants were excluded from this study.

Prior to the commencement of this study, the research protocol was approved by the Institutional review board (IRB). An informed written consent was taken from all the participants. Clinical, functional and radiological assessment at the first visit for all patients were recorded by full history taking, general examination and complete knee joint examination. The functional improvement of affected knee joint was assessed by IKDC subjective assessment form (2000) and the severity of pain was assessed by Douleur Neuropathique en 4 questions (DN4) and visual analogue scale (VAS). Plain X-ray of the affected knee, anteroposterior and lateral views was done for grading of knee OA according to the Kellgren–Lawrence grading system.

The participants were divided into two groups as follows: Group A= only platelet rich plasma (control group) = 40 patients, Group B= platelet rich plasma plus oral duloxetine (20mg) (experimental group) = 40 patients. Then, they were randomly assigned to

one of the two groups, using a computer generated random sampling and advised to take prophylactic oral antibiotic tab. Cefuroxime 250mg before starting of the procedure and to continue twice daily for 5 days. All procedures were performed by single skilled physician in operating room. After sterile dressing and draping intra articular injection was given to the patient in supine position with the knee partially flexed, using the lateral approach by 22 gauge needle. For group A patient immediately after introducing needle freshly prepared 5ml of autologous platelet rich plasma (PRP) was introduced and group B patient got 5ml of freshly prepared autologous PRP on affected joint plus cap Duloxetine (20mg) per oral daily for 12 weeks. After that, Cap Duloxetine (20mg) per oral was continued daily for 12 weeks. Both groups were transfused 3 cycle of PRP therapy in affected knee joint at 1 week interval. After injection, both group patients were instructed for early continuous passive movement to facilitate its diffusion and to apply local ice for 20 minutes every 2-3 hours for 24 hour and to avoid NSAID and vigorous activities for at least 48 hour.

Advises for the patients for maintenance of Activities of daily living instructions (ADLs) for knee osteoarthritis was given. All the principles of Good Clinical Practice (GCP) guideline for trials on pharmaceuticals products of Bangladesh were followed appropriately. Follow up was carried out by visiting in pain clinic at mentioned interval or over phone. To prevent confounding variables patient was closely supervised by his or her guardians. All patients have undergone follow-up examination after 1 week, 1 month, and 3 month by clinical assessment. Re-evaluation was done by IKDC subjective knee evaluation (2000) score for functional limitation, Severity of pain by visual analogue scale (VAS), and assessment of neuropathic pain by DN4 questionnaire.

Study measures

A pre-tested structured questionnaire was used for data collection. The questionnaire had two parts, demographic characteristics and assessment of pain and functional ability.

PRP: Platelet rich plasma (PRP) is a concentrated extract of platelets from autologous blood. Because

platelets have a high concentration of growth factors and cytokines within their alpha granules and dense granules, this makes PRP an appealing therapeutic alternative. It is as an autogenous source of growth factors like transforming growth factors (TGFs), connective tissue growth factors (CTGFs), insulin-like growth factors (IGFs), platelet derived growth factors (PDGFs), and fibroblast growth factors (FGFs), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF). Platelets are stimulated to release these growth factors and cytokines which are believed to influence the healing of the musculoskeletal system by promoting stem cells multiplication, collagen fibers synthesis, vasculogenesis, and articular cartilage repair, matrix synthesis, and cell proliferation²¹.

IKDC: The International Knee Documentation Committee (IKDC) Questionnaire is a knee-specific patient-reported outcome measure. It's considered to be one of the most reliable outcome reporting tools in its category. The entire IKDC form, which includes a demographic form, current health assessment form, subjective knee evaluation form, knee history form, surgical documentation form, and knee examination form, may be used as separate forms. The knee history form and surgical documentation form are provided for convenience. The IKDC Subjective Knee Evaluation Form is scored by summing the scores for the individual items and then transforming the score to a scale that ranges from 0 to 100. The reliability and responsiveness of IKDC are also comparable with other widely-used patient-reported outcome measures, particularly for those suffering from articular cartilage lesions. It is a fast and simple outcome tool. It requires just 10 minutes for completion and uses language that is easy to understand and suitable for all patient groups²².

DN4 questionnaire: The DN4 questionnaire was used to diagnose neuropathic pain. The French neuropathic pain group developed this clinician administered questionnaire named DN4 questionnaire consist of both sensory description and signs related to bedside sensory examination. This DN4 questionnaire is consists of 7 items related to symptoms and 3 related to clinical examination of the patient. The DN4 is easy to score and a total score of 4 or more out of 10 suggests neuropathic pain²³.

Visual analogue scale (VAS): It is a scale to assess pain intensity. It is marked in 0-10 according to intensity of pain. The criteria of vas will be follows: 0 (no pain), 1-2 (no pain at rest, mild pain on movement), 3-4 (mild pain on rest, moderate pain with movement and coughing), 5-6 (moderate pain at rest, severe pain with movement or coughing), 7-8 (severe pain at rest, acute pain with movement or coughing), 9-10 (acute pain on rest).

Ethical consideration

Prior to the commencement of this study, the research protocol was approved by Institutional review board (IRB). The aims and objective of the study along with its procedure, alternative diagnostic methods, risk and benefits were explained to the patients in easily understandable local language and then informed consent had been taken from each patient. It was assured that all records would be kept confidential and the procedure would be helpful for both the physician and patients in making rational approach regarding management of the case.

Statistical analysis

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean and median values were calculated for continuous variables. The qualitative observations were indicated by frequencies and percentages. Chi-Square test with Yates correction was used to analyze the categorical variables like sex, kellgren Lawrence grading and symptoms duration. For normally distributed data, Student t-test or fisher exact test was used. P values < 0.05 was considered as statistically significant.

Results

Total number of eighty (80) patients of knee osteoarthritis with neuropathic knee pain were recruited successfully. Recruited patients were equally divided into two groups A and B. Patients of group A selected for PRP in affected knee alone which is control group and group B selected for PRP in affected knee with oral Duloxetine which experimental group.

The average age was 51.65 ± 4.80 years in group A and 50.02 ± 4.36 years in group B. Majority were female between two groups which was 75% in group A and 72.5% in group B. Body mass index 26.56 in group A and 27.23 in group B. Kellgren Lawrence grade 25% were grade 1 and 75% were grade 2 in group A. On the other hand 5% were grade I and 95% were grade II. The duration of symptoms in group A, 42.5% were ≤ 12 months and 15% were in group B. But 57.5% were > 12 months in group A and 85% were in group B. (Table I)

Table I: Demographics of the study participants

Parameters	Group A (n=40)	Group B (n=40)	p value
Age (Years)	51.65 ± 4.80	50.05 ± 4.36	0.177
Sex			
Male	10(25.0%)	11(27.5%)	0.805
Female	30(75%)	29(72.5%)	
Body mass index(BMI)	26.56 ± 2.04	27.23 ± 1.58	0.103
Kellgren Lawrence grade			
Grade 1	10(25%)	2(5%)	0.103
Grade 2	30(75%)	38(95%)	
Symptom duration			
3 to 12 months	17(42.5%)	6(15%)	0.103
More than 12 months	23(57.5%)	34(85%)	

Values are expressed as Mean $\pm$ SD or absolute number. Within parentheses are percentages over column total. Statistical analysis was done using chi-square test or unpaired student's t-test where applicable p-value of <0.05 is considered as statistically significant.

In group A (control group), 16(40%) patients have local swelling of affected knee joint whereas 19 (47.5%) of all patients suffering local swelling of affected joint in Group B (experimental group). The difference was not statistically significant between the groups. In case of knee involvement, it was observed that more than half 23 (57.5%) patients had right side dominant knee involved in group A and 27(67.5%) in group B. The difference was statistically not significant ($p=0.356$) between the groups.

The mean IKDC score of pretreatment and 1st week in group A were 35.02 ± 3.52 and 36.23 ± 4.42 respectively and in group B were 32.82 ± 7.14 and 37.59 ± 6.85 . There was no statistically significant difference of mean IKDC score of pretreatment and 1st week between two groups ($P>0.05$). But the mean IKDC score of 1st month 45.60 ± 4.52 in group A and 50.92 ± 3.85 in group B. On 3rd months mean IKDC score in group A 47.53 ± 4.23 and 55.54 ± 4.64 in group

B. Mean IKDC score of both 1st and 3rd month were higher in group B than group A which was statistically significant between two groups ($p<0.05$). Figure 1 showed the mean IKDC score at different follow up.

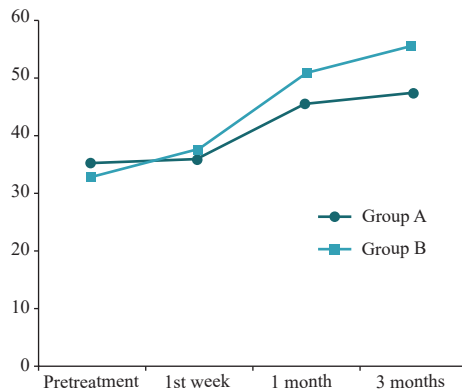


Fig. I: Mean IKDC score at different follow up

Table-II shows pretreatment DN4 score in group A and B were 7.45 ± 0.50 and 7.27 ± 0.45 respectively. In 1st week DN4 score in group A and B were 6.25 ± 0.58 and 6.22 ± 0.69 respectively. There were no statistically significant difference between two groups ($p>0.05$) in DN4 score. DN4 score of 1st month in group A 5.90 ± 0.77 and in group B was 3.95 ± 0.81 . On 3rd month there was further reduction of DN4 score which was 5.20 ± 0.51 in group A and 2.45 ± 0.59 in group B. The difference of DN4 score on 1st month and 3rd month in group B were much lower than group A which was statistically significant between the groups ($p<0.05$).

Table II: DN4 score at different follow up panel

	Group A (n=40)	Group B (n=40)	p value
Pretreatment	7.45±0.50	7.27±0.45	0.106 ^{ns}
1st week	6.25±0.58	6.22±0.69	0.863 ^{ns}
1st month	5.90±0.77	3.95±0.81	0.001 ^s
3rd month	5.20±0.51	2.45±0.59	0.001 ^s

Values are expressed as Mean±SD or number. Statistical analysis was done using chi-square test or unpaired student's t-test where p-value of <0.05 is considered as statistically significant

The mean VAS score at pretreatment in group A were 6.80 ± 0.60 and 1st week 6.60 ± 0.63 whereas in group B 6.87 ± 0.64 and 6.35 ± 0.69 respectively. There were no statistically significant difference between two groups ($p>0.05$) in mean VAS score. But 1st month and 3rd months were lower mean VAS score in group B (4.05 ± 0.67 and 2.15 ± 0.36 respectively) than group

A (5.75 ± 0.43 and 4.75 ± 0.43). The reduction of mean VAS score on 1st and 3rd month statistically significant between two groups ($p<0.05$). Figure 2 showed mean VAS score at different follow up.

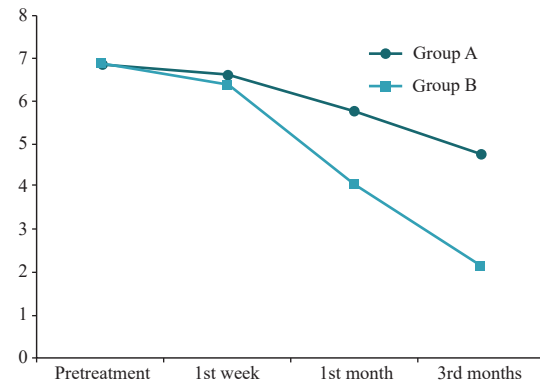


Fig. II: Mean VAS score at different follow up interval

Discussion

This randomized clinical trial was carried out with the aims to assess the reducing of neuropathic pain and improvement of functional outcome in knee osteoarthritis using oral duloxetine in addition with platelet rich plasma (PRP) compare with therapeutic effect of platelet rich plasma (PRP) alone, been evaluated by Douleur Neuropathique en 4 questions (DN4) and visual analog scale (VAS) for improvement of pain and functional outcome by international knee documentation committee (IKDC) score.

In this present study mean age was almost alike between two groups, the difference was not statistically significant ($p=0.177$) between two groups. It was observed age ranged varied from 40 to 70 years with a mean of 50.4 ± 8.0 years²⁴. Similar age ranged was also observed by other studies^{20,25}. In this study we enrolled patient between the ages of 40 to 60 years due to inclusion criteria of the study. Reason behind such selection of age group, is the presence of high percentage of living and vital cells in young patient and therefore the high response potential to the growth factors of platelet rich plasma²⁴.

Female predominance was observed in this study and the gender difference was not statistically significant ($p = 0.461$) between two groups. In contrast Lana et al.2016²⁶ observe 91.7% patients were female in

group A, 80.6% in group B and 81.8% in group C. In another study²⁴ found 70.0% females and 30.0% males, which is similar with the current study. Female are more prone to suffer knee osteoarthritis due to their occupational hazards, poor nutritional status, insufficient rest, minor injuries from daily activity and hormonal imbalance in our country.

The mean body mass index (BMI) in the population of this study in both group were higher than normal but almost alike between two groups, the difference was not statistically significant ($p=0.103$). Demographic variables and anthropometric parameters were almost identical between two groups in this study, no significant difference was observed between two groups. Lana et al.2016²⁶, found the mean BMI was $28.24 \pm 8.77 \text{ kg/m}^2$ in hyaluronic acid (HA) group, $27.42 \pm 6.89 \text{ kg/m}^2$ in platelet rich plasma (PRP) group and 29.15 ± 7.31 in group PRP and HA combination group, which is slightly higher than the current study maybe due to geographical variations and higher body surface area in their study patients. A prospective study conduct on 823 patients for 22 years found that BMI was strongly associated with the risk of developing osteoarthritis of the knee, independent of covariates like age and gender²⁷.

Obesity is associated with the prevalence and morbidity of knee OA and is one of the major risk factor for Knee OA. Overweight can increase the joint load and have a detrimental effect on weight-bearing joints. Excessive fat can cause degenerative changes in articular cartilage by subjecting it to more than biomechanical pressure²⁸.

In this current study functional outcomes were evaluated using the International Knee Documentation Committee (IKDC) scores. In this study mean IKDC score of 1st month and 3rd month statistically significant ($p<0.05$) between group A and group B. At 1st week mean IKDC score almost identical between the groups. There were gross improvements of IKDC score in both groups at the end of 1st month but in group B IKDC score increases significantly than group A. There were more increases of IKDC score at 3rd month in group B than A which was also statistically significant ($p<0.05$) between the groups. In this study affected knee functional status was evaluated by IKDC scoring system. Other

studies²⁹ also showed gross improvement of IKDC score in the patients treated with the combination of PRP and micro fractures than micro-fracture alone at all follow-up period which is similar to this study.

Similarly in prospective study³⁰, where WOMAC scores were used for evaluation of functional status of affected knee. In this study all the patients have shown decrease in the WOMAC score in both follow up period. Their mean pain, stiffness and functionality scores have decreased. The decrease in WOMAC score continued upto six months. The improvement in our patients could be explained by the fact that injected platelets might have acted at different levels and were not stimulating the chondral anabolism or slowing the catabolic process. The results showed better improvement in grade I osteoarthritis knee joints than grade II knee joints.

Intra-articular PRP injection in patients with knee OA showed significant improvement in pain relief, improvement of symptom and quality of life. Due to the immediate and sustained release of growth factors over a long period of time, PRP can promotes healing and produces sustained clinical effects. Similarly it was found that, PRP can significantly improve the prognosis of patients 6 months after injection, and these improvements began in 2 months and lasted for 12 months³¹.

There are several scoring system to identify neuropathic pain among them DN4 score is effective one. So DN4 questionnaire score used in this study to identify and assessment of neuropathic pain in knee osteoarthritis. Mean DN4 score of this study in 1st month and 3rd month were in group B less than group A which was statistically significant between two groups ($P<0.05$). A study conducted on 161 patients with knee OA found high DN4 score in both group A and B that indicate patient of chronic knee osteoarthritis suffering from neuropathic pain³². In this study for the treatment of neuropathic pain Duloxetine was used in group A. Reduce DN4 score in group A in 1st and 3rd month reflect the efficacy of Duloxetine to combat neuropathic pain similar result also found in this study.

A study conducted on 256 patients who had suffered from chronic pain from knee OA. Where 111 (86.7%)

in placebo group and 93 (72.7%) in duloxetine group. They showed patients treated with duloxetine had significantly ($P < 0.001$) greater improvement at all-time points on BPI average pain and had significantly greater improvement on BPI pain severity ratings ($P < 0.05$), WOMAC total ($P = 0.044$) and physical functioning scores ($P = 0.016$), and CGI-S ($P = 0.009$) at the study endpoint. Treatment with duloxetine was associated with significant pain reduction and improved function in patients with pain due to osteoarthritis of the knee³¹.

Similar another study, conducted on 524 patients who suffered from knee OA randomly, received duloxetine or placebo. After completion of study they showed Duloxetine- treated patients had significantly greater pain reduction at week 8 ($p < 0.001$) than placebo-treated patients. In addition, relative to placebo at week 8, duloxetine-treated patients had significant improvements in physical function as measured by the Western Ontario and McMaster Universities Osteoarthritis Index ($p < 0.001$), and Patient Global Impression of Improvement ($p < 0.001$)³³.

On the other hand mean Visual Analogue Score (VAS) of this trial at pretreatment ($P = 0.106$) and 1st ($P = 0.863$) week were not significantly different between two groups statistically. But VAS score on follow up period of 1st month revealed statistically significant ($p < 0.05$) reduction in group B than group A. On follow up period of 3rd month further reduction of VAS score in group B than in group A which was also statistically significant ($p < 0.05$) between two groups.

A comparative study, compared HA and PRP combination versus PRP monotherapy versus HA in mild to moderate knee osteoarthritis. Outcome was evaluated by VAS and WOMAC score. Their result showed better outcomes in the HA and PRP combination group over HA alone up to one year and over PRP alone up to three months²⁶.

In this study duloxetine with PRP used in group A to improve neuropathic pain along with improvement of functional status and quality of life of the patients suffering from knee OA. Another study suggests duloxetine may be efficaciously reduce knee pain

associated with osteoarthritis and is well tolerated in this patient population. It also implicated that adding duloxetine to the repertoire of osteoarthritis pain treatments has the potential to benefit a large and growing number of patients, many of whom have experienced intolerable adverse events or inadequate analgesia with other classes of drugs. The positive outcome of this study suggests that duloxetine is effective in the treatment of centrally mediated chronic pain as a centrally acting analgesic¹⁴.

In very recent, a study conducted on patient suffering from knee OA which divided the patient in two groups. One group was assigned for PRP and for Hyaluronic acid injection. They measured WOMAC, EQ-VAS, VAS, IKDC, and other evaluation tools, different results can be seen in different months. They found that the symptoms of patients in HA and PRP groups improved significantly in the first two months, and the improvement between the two groups was similar (according to WOMAC scores, EQVAS). However, after 3 months of follow-up, in WOMAC scores, the PRP group was superior to the HA group in terms of joint stiffness relief and body function recovery. At 12th month, according to VAS, EQ-VAS and WOMAC scores, PRP was superior to HA in pain relief and functional improvement³⁴ which is supportive of this study.

So, concomitant use of Duloxetine with PRP potentiate the therapeutic effect of PRP, significantly reduce pain severity, causes early reduction of VAS score and DN4 score along with improvisation of IKDC score of patient suffering from chronic knee osteoarthritis.

Conclusion

Intra articular platelet rich plasma in combination with oral duloxetine provide better pain relief and improvement of functional status than PRP alone in chronic knee osteoarthritis with neuropathic pain. Therefore, platelet rich plasma plus oral duloxetine may be an alternative therapy in selective patients resistant to current pharmacological and non-pharmacological therapies.

Declaration

Ethics approval

The study was approved by the Ethical Review Committee of BSMMU. Informed written consent was taken from the participants before inclusion.

Author contributions

Conception and development of the idea *AKMA*, *MM*
Writing *MM*, *SAM*

Data analysis *MM*, *MMK*

Data collection *MM*, *MNI*, *SS*

Review and Editing *MM*, *MMK*, *AKMA*

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Conflict of interests None

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