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ORIGINAL ARTICLE

The short-term effect of PRP on chronic pain in knee osteoarthritis

Diz osteoartritinde PRP'nin kronik ağrı üzerine kısa dönem etkinliği

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Summary

Objectives: The administration of platelet-rich plasma (PRP), which increases the release of growth factors targeting cartilage regeneration, is used in an effort to relieve pain in knee osteoarthritis (OA). This study measured the short-term efficacy of PRP on chronic pain in patients with OA of the knee.

Methods: Patients with chronic knee pain and grade 2-4 knee OA based on the Kellgren-Lawrence (K-L) classification were enrolled in the study. A total of 60 knee joints of 42 patients who completed 3 doses of intraarticular PRP injections administered at intervals of 3 weeks were analyzed. The patients' pain was evaluated using a resting and activity visual analog scale (VAS) on day 0, and at week 3, 6, and 12.

Results: Of the 42 patients, 37 were female. The mean age and body mass index was 60.52±10.41 years and 28.5±9.71 kg/m2. A total of 18 patients had bilateral knee involvement, and 39 of the 60 knee joints were classified as K-L grade 3-4 OA. A significant improvement was observed in the mean resting and activity VAS scores at day 0 and week 12 ($p<0.05$). In K-L grade 2 patients, the day 0 and week 3 resting and activity VAS scores were significantly better than the grade 3-4 scores ($p<0.05$).

Conclusion: It was observed that PRP injections provided a meaningful improvement in chronic knee pain in patients with knee OA throughout a 12-week period. The pain reduction response to PRP was better in patients with early-stage knee OA.

Keywords: Chronic; knee; osteoarthritis; pain; platelet-rich plasma.

Özet

Amaç: Diz osteoartritinde (OA) kıkırdak rejenerasyonu sağlamaya yönelik büyüme faktörlerinin salınımını artıran platelet rich plasma (PRP) uygulamaları ile diz ağrılarında iyileşme sağlanmaya çalışılmaktadır. Biz de bu nedenle diz OA'da PRP'nin kronik ağrı üzerine kısa dönem etkinliğini ölçmeyi amaçladık.

Gereç ve Yöntem: Kellgren – Lawrence (K-L) sınıflamasına göre grade 2-4 arası diz OA olan kronik diz ağrılı 69 hasta çalışmaya alındı. 3 hafta aralıklarla uygulanan 3 doz intraartiküler PRP enjeksiyonunu tamamlayan 42 hastanın 60 diz eklemi ile çalışma tamamlandı. Hastaların ağrıları 0. gün, 3., 6., ve 12. haftalarda istirahat ve aktivite visual analog scala (VAS) ile değerlendirildi.

Bulgular: 37'si kadın 42 hastanın ortalama yaşı ve vücut kitle indeksi sırasıyla (ort±standart sapma (SS)) 60.52±10.41 ve 28.5±9.71 idi. Toplam 18 hasta bilateral diz olup, 60 diz ekleminin 39'u ise K-L grade 3-4 osteoartritti. Hastaların 0. gün ve 12. hafta ortalama istirahat ve aktivite VAS skorlarında; (sırasıyla (ort±SS), 5.13±2.70, 7.68±1.83 ve 2.60±2.05, 3.75±2.12, $p<0.05$) anlamlı iyileşme görüldü. K-L grade 2 hastalarda 0. gün ve 3. hafta istirahat ve aktivite VAS (sırasıyla (ort±SS), 3.43±1.50, 6.81±1.28 ve 2.57±1.59, 4.10±1.84) skorları grade 3-4'e (sırasıyla (ort±SS), 6.05±2.77, 8.15±1.92 ve 4.49±2.22, 5.74±1.61; $p<0.05$) göre anlamlı daha iyi olup, 6. ve 12. Hafta istirahat ve aktivite VAS (sırasıyla (ort±SS), 2.38±1.85, 3.29±1.82; 3.36±1.76, 4.03±1.54 ve 2.14±1.82, 3.19±2.31; 2.85±2.14, 4.05±1.97; $p>0.05$) skorlarında anlamlı bir fark yoktu.

Sonuç: Diz osteoartritinde PRP enjeksiyonlarının 12 haftalık takip döneminde kronik diz ağrıları üzerine anlamlı düzelme sağladığı görüldü. Ek olarak, erken evre diz OA'lılarda PRP'ye ağrıda azalma yanıtı daha iyi bulundu.

Anahtar sözcükler: Ağrı; diz; kronik; osteoartrit; PRP.

Introduction

Osteoarthritis (OA) is the most frequent chronic knee disease.[1] On the histopathology of OA, the joint becomes degraded as a result of the shift in the balance between injury and repair mechanisms in favor of inflammatory cytokines (IL-1, TNF-alpha) and the deficiency of the synthesis of anti-inflammatory cytokines (IL-4, IL-10).[2, 3] Knee osteoarthritis is a significant health issue common in old age that runs with pain and functional limitations. It has been reported that conservative treatments (physical therapy practices, topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), and intraarticular (IA) injections) increase the life quality of patients, particularly at early stages

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of knee osteoarthritis.[4-9] Because these non-surgical conservative treatment methods have certain handicaps such as short-lasting effectiveness and some systemic and local side effects, new approaches to the treatment of OA have been sought. In this regard, it has been focused on the fact that growth factors and cytokines stimulate the cartilage regeneration processes, particularly in recent studies.[1, 4] In the last decade, IA platelet rich plasma (PRP) injections have started being used in the treatment of OA.[10, 11]

PRP is a thrombocyte rich concentrate of plasma obtained by the centrifugation of autologous blood. Platelets contain high amounts of growth factor (GF) and cytokines. It is believed that the delivery of high concentrations of cytokines and GFs to the injured area by PRP leads to regeneration of the cartilaginous tissue and that it has anti-inflammatory effects.[10, 12, 13] Studies that investigate these regenerative and anti-inflammatory effects of PRP, particularly as a potential treatment of OA have been conducted.[13-15] Despite this, clinicians still have many questions about the application of PRP. These are the differences between the methods used to obtain PRP, the number of injections, and the application times of the injections. It is being recommended to perform more studies to identify the optimal number, duration, and methods of applying PRP injections and to define their clinical benefit.[5]

With this goal, in our study, we aimed to determine the effect of PRP injections on pain in chronic knee osteoarthritis by delivering a total of three PRP doses at intervals of three weeks.

Materials and Methods

Participants

The patients included individuals that applied to the Physical Therapy and Rehabilitation clinic of the Private Bagcilar Aktif Medicine center with chronic knee pain persisting for longer than three months between 40 and 80 years of age who were diagnosed with osteoarthritis based on the American College of Rheumatology (ACR) criteria[16] and followed as outpatients. The study conducted between January 2016 and June 2017 enrolled patients with grade 2-4 knee osteoarthritis based on the Kellgren-Lawrence (K-L) classification[17] who provided voluntary informed consent. Exclusion and inclusion criteria have been given in table 1. Approval for the study was obtained from the medical faculty Ethics Committees (No: 83045809/604.01/02, date: 07.10.2015).

Interventions

Although there is no clear data about the number of PRP injections in the treatment of OA, we performed a total of three IA PRP injections at intervals of three weeks which is the most common use in the practice of our country. Approximately 10 mL of blood was taken from patients for each knee and was revolved at 3000 rpm for 8 minutes. By doing so, approximately 4 mL of leukocyte-poor PRP was obtained. The PRP prepared was injected into the knee involved within twenty minutes. Injections were performed with patients sitting with their legs swinging down from the gurney with their knees at approximately 80 degrees of flexion. The injection was performed after identifying the borders of the patella by palpation and marking the skin anterolateral to the joint space and maintaining antisepsis. To clearly determine that we were inside of the joint during the injection, we made sure that the plasma advanced into the joint space without any resistance and that there was not too much pain. The patients were instructed to limit

Table 1. Patient screening criteria

Inclusion Criteria
• Age between 40 and 80 years
• Pain that lasts more than 3 months
• Grade 2-4 radiographic OA as defined by the K- L classification
Exclusion Criteria
• Knee instability
• Severe trauma to the affected directory in the near future
• Active infection, inflammation or tumor presence around the knee
• Systemic disorders such as diabetes, rheumatoid arthritis, hematological diseases (coagulopathies), severe cardiovascular diseases, infections, or immunodeficiencies
• Current use of anticoagulant medications or NSAIDs used in the 5 days before blood donation
• Hb values <11 g/dl or platelet counts <150.000 / micro liter,
• Recent intra-articular injection of corticosteroids, HA, ozon or PRP in past 6 months
• Pregnancy or lactation

*HA: hyaluronic acid; PRP: platelet rich plasma; K-L: Kellgren-Lawrence; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; Hb: hemoglobin.

the use of leg for at least 24 hours after treatment and to apply icepacks three times a day for twenty minutes on the first two days. During this treatment period, the patients performed resting or mild exercise activities and slowly returned to daily life activities as much as was tolerated.

Outcome measures

The clinical and demographic characteristics age, gender, education level, physical examination findings, duration of complaints, drug use, secondary diseases, and surgical history of patients were recorded. The patients were graded based on the K-L classification, and two groups were formed as the grade 2 and grade 3-4 groups. The data analysis was also performed based on these groups. To measure the main objective of the study the patients' pain was assessed by a physiatrist not included in the study on day 0 (the day of the first PRP injection), week 3 (the day of the second PRP injection), week 6 (the day of the third PRP injection) and week 12 using the visual analog scale (VAS) at resting and activity. VAS assessment was done with numbers from "0" to "10", equidistantly marked on a 10-cm line. The patients were explained that "0" meant they were experiencing no pain, "5" moderate pain and "10" unbearable pain, and they were asked to mark the appropriate score on the line describing their own pain during rest and physical activity.[18] Adverse events (pain, swelling, redness, or difficulty walking were questioned during PRP injections and at follow-up dates. The study was completed with the patients that completed the 12-weekperiod, and statistical analyses were performed.

Statistical Analyses

All statistical analyses were performed using the SPSS for Windows software package (ver. 22.0; SPSS Inc., Chicago, IL, USA). All data are presented as arithmetic mean±standard deviation (SD). The normality of data was assessed using the Shapiro-Wilk test. Paired samples and Independent samples t-tests were used to compare normally distributed variables, and non-parametric Mann-Whitney U and Wilcoxon tests were used to compare non-normally distributed variables. The Mann-Whitney U test was also used to compare groups (between-group comparison). The Wilcoxon test was used to compare the results of tests performed before and after treatment (within-group comparison). For all analyses, a value of $p<0.05$ was considered to indicate statistical significance.

Results

Seventy-six patients with chronic knee pain were assessed for the study. Seven patients were dropped because they did not accept to participate in the study or because they did not meet the study inclusion criteria. The study was launched with 88 knee joints of 69 patients. After the first PRP injection 5, and after the second PRP injection 11 patients were lost to follow-up; the third PRP injection was delivered to 71 knee joints of 53 patients. A total of 241 PRP injections were performed. The study was completed with 60 knee joints in 42 patients who had received three PRP injections that attended the last follow-up at week 12, and the statistical analysis was performed (Fig. 1).

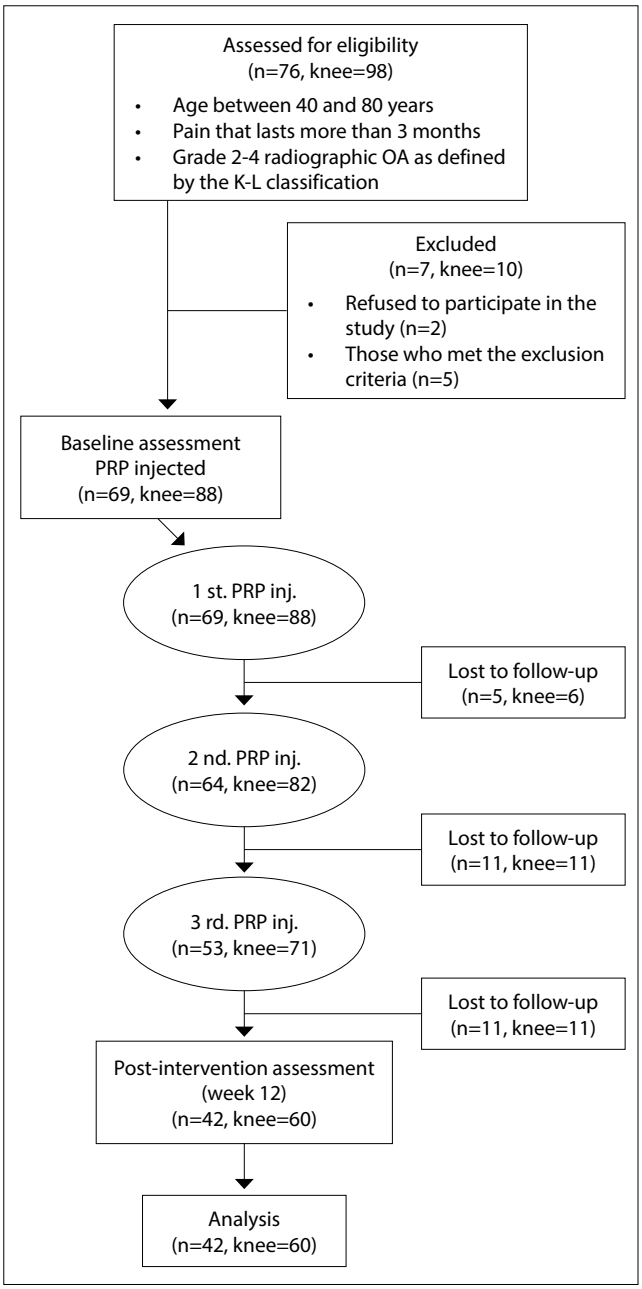

Figure 1. Study flow chart.

The mean age and body mass index (BMI) of the 42 patients of which 37 were female were 60.52±10.41 and 28.5±9.71 respectively. A total of 18 patients had bilateral knees involved, and 60 of the 39 knee joints were K-L grade 3-4 osteoarthritis (Table 2).

In the 60 knee joints of 42 patients the mean resting and activity VAS scores (mean±SD) on day 0 before treatment and at 12 weeks were 5.13±2.70, 7.68±1.83 and 2.60±2.05, 3.75±2.12 respectively (Fig. 2). The improvement of resting and activity VAS scores on day 0 and week 12 was 2.53±2.09 and 3.93±2.15, respectively, and a statistically significant improvement was observed ($p<0.05$) (Table 3). In the comparison of the grade 2 and grade 3-4 patient groups the improvements in the VAS scores were 1.28±1.18, 3.61±2.08 and 3.20±2.17, 4.10±2.19, respectively, and a statistically significant improvement was also observed (Table 3).The changes in the resting and activity VAS scores and the recovery rates of the patients at day 0, week 3, 6, and 12 are presented as a graphic in figure 2. This graphic shows a statistically significant improvement in the amount of reduction of the resting and activity VAS scores until week six ($p<0.05$). However, it appears that the change between week 6 and 12 is not meaningful and that the VAS scores form a plateau ($p>0.05$) (Fig. 2). Besides this, while the comparison of the resting and activity VAS scores of the groups of grade 2 and grade 3-4 showed high VAS levels in favor of grade 3-4 on day 0 and week 3, no meaningful difference was detected between the scores at week 6 and 12 (Table 4).

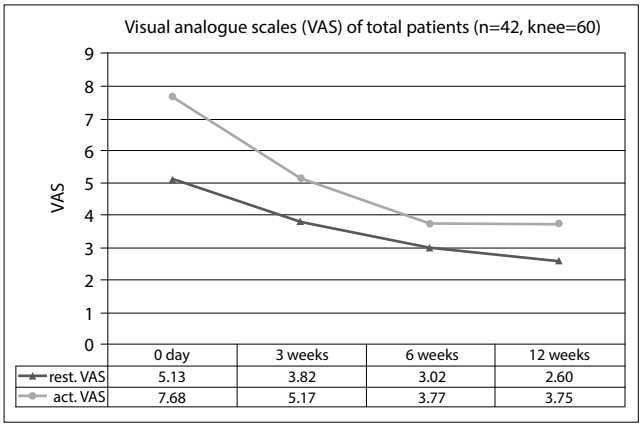

Figure 2. The changes in the resting and activity VAS scores.

Table 2. Clinical and demographic characteristics

Total number of patients (n)	42
Gender (n)	
Male	5
Female	37
Age (mean±SD)	60.52±10.41
BMI (kg/m^2) (mean±SD)	28.5±9.71
Injection side (n)	
Right	14
Left	10
Bilateral	18
Injected total knee joint	60
K-L grade	
2	21
3	29
4	10

K-L: Kellgren Lawrence; n: Number of patients; SD: standart deviation.

Table 3. Rates of improvement in VAS scores pre- (0 day) and post-(12 weeks) treatment

	Follow- up period	Total patient (mean±SD)	K-L grade 2 (mean±SD)	K-L grade 3-4 (mean±SD)	p
rest. VAS	0 day	5.13±2.70	3.43±1.50	6.05±2.77	0.000*
	12 weeks	2.60±2.05	2.14±1.82	2.85±2.14	0.278
	imp.	2.53±2.09	1.28±1.18	3.20±2.17	
	p	0.000*	0.001*	0.000*	
act.VAS	0 day	7.68 ±1.83	6.81±1.28	8.15±1.92	0.003*
	12 weeks	3.75±2.12	3.19±2.31	4.05±1.97	0.152
	imp.	3.93±2.15	3.61±2.08	4.10±2.19	
	p	0.000*	0.000*	0.000*	

K-L: Kellgren Lawrence; VAS: visual analog scale; imp: rates of improvement; SD: standart deviation; rest: resting; act: activity; *p<0.05.

Statistical tests used in this table: Wilcoxon test (non-normally distributed) and Paired samples test (within-group comparison), Independent samples t-test and ManWhitney U test (non-normally distributed) (between-group comparison).

Table 4. K-L grade 2 and 3-4 rest and activity VAS comparative

Follow-up period	VAS	K-L grade	N	Mean±SD	p
0 day	rest.	2	21	3.43±1.50	.000*
		3-4	39	6.05±2.77	
	act.	2	21	6.81±1.28	.002*
		3-4	39	8.15±1.92	
3 weeks	rest	2	21	2.57±1.59	.000*
		3-4	39	4.49±2.22	
	act.	2	21	4.10±1.84	.001*
		3-4	39	5.74±1.61	
6 weeks	rest.	2	21	2.38±1.85	.055
		3-4	39	3.36±1.76	
	act.	2	21	3.29±1.82	.123
		3-4	39	4.03±1.54	
12 weeks	rest	2	21	2.14±1.82	.188
		3-4	39	2.85±2.14	
	act.	2	21	3.19±2.31	.157
		3-4	39	4.05±1.97	

K-L: Kellgren Lawrence; VAS: visual analog scale; N: Number of patients; SD: standart deviation; act: activity; *p<0.05. Statistical tests used in this table: Independent samples test.

The adverse events recorded in a total of 241 PRP injections were pain and mild swelling in the knee in 8 patients (that resolved with 3 days of rest, cold application, and simple analgesics) and hypotension syncope that occurred in 1 patient. None of the adverse events were specific and all resolved completely. NSAID use after PRP injection was not permitted.

Discussion

The interest in treatments targeting healing injured cartilage in knee OA with dominant pain symptoms has increased in recent years.[1, 4] PRP which is often used for this purpose aims to stimulate cartilage repair, improve life quality, and reduce pain in knee osteoarthritis.[19]

The presence of leukocytes in PRP, the frequency and interval of PRP administration, and the number of thrombocytes are topics still being debated.[1, 4] The thrombocyte concentration and the amount and effectiveness of thrombocyte related growth factors vary based on the PRP preparation technique. In the literature, it has been reported that the platelet concentration of PRP should be at least 1-fold higher than it is in full blood.[20] Using the PRP technique applied in our study platelets were obtained at a concentration 3-4 times higher than it is in full blood. This was similar to the concentrations recommended and used in many studies.[21]

In debates about the use of leukocytes in PRP, it is believed that neutrophils reveal the metalloproteins and free radicals that degrade the extracellular matrix and that they also increase the inflammatory activity in the joint.[22] In this aspect, to prevent leukocytes from causing joint damage or excessive anti-inflammatory responses leukocyte-poor PRP was used in our study.

In literature, different results are reported about the K-L grade and response to PRP treatment in knee osteoarthritis.[3, 23-25] However, today the prominent opinion is that PRP responses are better in low K-L grade patients with little joint and cartilage degeneration.[1, 3, 5]

Factors such as the reduction of living cells and the anabolic response to growth factors, the loss of chondrocytes, the thinning of the cartilage plate, deficient muscular functions and joint instability due to increased ligament laxity could reduce the effectiveness of PRP as joint degeneration increases.[1, 12] It is believed that PRP might not have any direct effect on the anabolic process in chondrocytes in the advanced stages of OA but that it may have an anti-inflammatory effect through the regulation of common homeostasis and cytokine levels.[9, 26] In this regard, some studies have reported that advanced stage OA patients also benefit from PRP although the response is weaker.[1, 23] Calis et al.[27] reported that PRP was delivered to patients with grade 3-4 knee OA three times at weekly intervals and showed that the thickness of cartilage measured by ultrasonography at the 6-month follow-up was increased. Whereas, Kavadar et al.[1] reported that PRP was effective on pain and physical functions in grade 3 knee OA. However, in our study, it is seen that PRP is effective on pain in patients with grade 2 and grade 3 knee OA within the 3-month period but that the pain scores plateau after week 6. Besides this, although the pain response to PRP was better in favor of grade 2 within

the six-week period, no difference was observed after the sixth week.

The heterogeneity of PRP doses and durations in the related literature is excessive, and standardization has not been accomplished yet. The lack of standardization of the PRP dose regimens makes it challenging to compare the results of studies performed to evaluate clinical effectiveness.[28] Kavadar et al.[1] reported that 3 sessions of PRP injections performed at two-week intervals in grade 3 knee OA were more effective than single or double injections and that the effect observed after the first injection rapidly diminishes. Besides this, they recommended repeating PRP injections six months later to delay the progression of OA and to suppress the symptoms for longer. Likewise, Patel et al.[24] verified that single or double PRP injections are more effective than placebo, but that results deteriorate within 6 months. In the studies, it has been shown that the improvement in OA symptoms after PRP applications can continue for up to 24 months even if the first 3 months have started to decrease.[22, 29, 30]

On the other hand, in our study, we performed a total of three IA PRP injections at intervals of three weeks which is the more common practice in our country. Although meaningful improvements were observed in VAS pain scores over the 12-week follow-up period, the pain response formed a plateau starting from the sixth week. As a limitation of our study, the effect of PRP on pain was not assessed in following months because the follow-up period was short. However, we anticipate that this plateau that appears after the sixth week will accelerate upwards in following months as the effect of treatment decreases. In this regard, we recommend repeating the PRP injection six months later and performing control examinations of these patients every six months. When studies that compare PRP to other IA injection types are reviewed, it is especially possible to encounter HA studies. In a systematic review that included 14 randomized controlled trials (RCT), the effect of PRP on knee pain and physical functions in knee OA was compared to other injections such as saline, HA, ozone, and corticosteroid injections. It was observed that PRP demonstrated superiority at 3, 6, and 12 months after treatment.[10] However, because we did not have a control group to compare the PRP injections to in our study, we were unable to perform comparisons to other injections.

Some adverse events were encountered in studies performed with PRP injections. However, there is no substantial increase in comparison to other IA injections.[10] These side effects are non-specific self-limiting adverse events such as arthralgia, arthritis, dizziness, sweating, tachycardia, and syncope.[10] Likewise, non-specific, rapidly recovering similar adverse events were encountered in our study and no severe side effects developed.

This study has certain limitations. The most significant is the lack of a control group. The second is the failure to rule out the placebo effect which has been reported to be important in alleviating pain in the treatment of OA. One other limitation is the fact that the study results are based on patient reported VAS scale data which could potentially limit the objectivity of the study results. Although more objective results about treatment response could have been obtained through assessments performed using functional tests, these tests were not used in our study. Despite these limitations, the strengths of our study were the assessment of the patients' pain scores by an independent observer who was not part of the study, the sufficiency of the 12-week follow-up for evaluating short-term pain response, and the consistency of the number and duration of PRP injections in our study with literature.

Conclusion

It was observed that PRP injections provide a meaningful improvement in chronic knee pain in knee osteoarthritis throughout a 12-week period. However, it was identified that this improvement runs a stable course between week 6 and 12. Besides this, the pain reduction responses of K-L grade 3-4 knee osteoarthritis was found to be less meaningful when compared to grade 2 patients.

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