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Comparison of intra-articular platelet-rich plasma injection versus placebo for clinical outcomes in patients with knee osteoarthritis; a double-blind, randomized trial

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Abstract

Introduction: Osteoarthritis (OA) is a progressively debilitating condition that leads to musculoskeletal pain, particularly in the knee joint. Most clinical guidelines recommend platelet-rich plasma (PRP) for knee OA. However, the use of PRP in knee OA is increasing.

Objectives: This study aimed to investigate the effects of intra-articular administration of PRP on the symptoms, lower limb function, and daily living activities in patients with knee OA.

Patients and Methods: A double-blind, randomized, controlled clinical trial was conducted and 34 patients with grade 2 or 3 knee OA were enrolled. The knees of each participant were randomly allocated to receive either 3cc PRP injection (PRP knees) or needling only (control knees). Patients were evaluated by a general practitioner before, three, and six months after the intervention using the EuroQol-visual analog scales (EQ-VAS), the International Knee Documentation Committee (IKDC), the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the Tegner Activity Score (TAS).

Results: The mean (±SD) age of patients with knee OA was 56.6 ± 10.2 years. Seventy-point-six percent of patients were female. 67.6% and 32.4% of patients were in stages 2 and 3 of the disease, respectively. IKDC, WOMAC, TAS, and EQ-VAS scores in knees under PRP injection and control of knees, three and six months after injection showed significant improvement. Three and six months after the intervention, IKDC, WOMAC, TAS, and EQ-VAS scores in the PRP and control knees were not significant ($P > 0.05$). Inter-group comparison indicated that the IKDC score significantly increased six months in comparison to three months ($P = 0.048$) in PRP knees, but not significant in the control knees ($P = 0.133$). TAS score in PRP and control knees significantly increased six months compared to three months after injection. WOMAC and EQ-VAS score in PRP and control knees was not significant at six months in comparison to three months after the intervention.

Conclusion: Our findings could suggest safety and feasibility data for the intra-articular administration of PRP in patients with knee OA that may help to appraise a larger clinical trial. Findings show that PRP injection improves IKDC, WOMAC, TAS, and EQ-VAS scores, however, there was no significant difference with needling only (control knees).

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trial (identifier: IRCT2015010112823N2; https://en.irct.ir/trial/12827, Ethics committee reference number: 93/551664) and Research Registry (Research Registry Unique Identifying Number: researchregistry9843).

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Introduction

Osteoarthritis (OA) is a progressively debilitating condition that leads musculoskeletal pains especially in knee joints in all over world (1). Knee OA is a progressive disease involving the patella-femoral cartilage, intra-articular tibia-femoral, periarticular structures and all other surrounding intra-articular (2). It is predicted to the prevalence of knee OA over the next 25 years is increased parallel to the increase in the elderly population and growing rates of obesity by approximately 6-folded (3). With regards to the associated risk of joint replacements with implant wear and a limited lifespan for joint revision surgery, more attention

Key point

Our double-blind, randomized, controlled clinical trial suggested that intra-articular administration of PRP in patients with knee osteoarthritis improved the osteoarthritis pain and patient's physical activity.

has been paid to the use of conservative interventions in the younger and middle-aged population with knee OA and cartilage damage (4). Conservative nonsurgical interventions have been delaying total knee arthroplasty and indicated to treat the painful knee joint. Treatments involving oral nonsteroidal anti-inflammatory drugs (NSAIDs); intra-articular administration into the knee joint, such as the administration of corticosteroids and hyaluronic acid; unloader bracing, and physical therapy play major roles in the nonsurgical management of knee OA (5). Pharmacological therapies including steroid anti-inflammatory drugs, NSAIDs and corticosteroid injections often have side effects and provide only temporary benefit (6). The interventions are efficient and profitable, but these have a few limitations. Non-pharmacological interventions, including lifestyle modification and exercise are commonly related to poor compliance. The existing therapies have limitations, and on the other hand, the nature of knee OA is progressive, so finding an appropriate method to control and treat this disease, even in the short term, is of particular importance (1).

Some studies have suggested that cytokines and growth factors secreted from platelets in response to pathology or injury may contribute to the regeneration or maintenance of tissue structures and modulate inflammatory processes (7). The administration of platelet-rich plasma (PRP) improves soft tissue healing in some disorders which related to bone mineralization, tendon and ligament injury and cartilage regeneration (8). Platelet-derived growth factors, stored in granulate of PRP and regulate some biological mechanisms in tissue regeneration (9). The efficacy of the intra-articular administration of the PRP into knee OA was investigated in some studies and indicated to clinical improvement of symptoms and self-reported pain intensity, It without complications and any significant adverse effects (10). A systematic review investigated six clinical trial studies on the efficacy of the intra-articular administration of PRP into knee OA (4), only two studies were designed in form of a double blinded with a matched control (11, 12). The studies did not evaluate the objective measures of administration of the PRP on lower extremity function. However, a number of un-blinded and non-randomized pilot and prospective studies have demonstrated negative and positive outcomes and the experimental data are rather controversial, without any general agreement (4). This has made it impossible to say with certainty whether this method has the benefit for symptom relief and improvement of movement status or not (13). Therefore, more studies are needed in this area.

Objectives

This randomized, double-blind, controlled pilot study was conducted to investigate the efficacy of administering PRP on the safety, feasibility, and improvement of symptom severity, lower limb function, and function in daily living activities in patients with mild to moderate stages of knee OA.

Patients and Methods

Trial design

In a randomized, double-blind controlled clinical trial, patients referred to the Rheumatology clinic at Semnan university of medical sciences, Semnan, Iran, between January and July 2016 were enrolled after informed consent. The knees of each participant were randomly allocated to receive either 3 cc PRP injection (PRP knees) or needling only (control knees) using computer-generated random numbers.

Participants

Based on guidelines for pilot studies, 34 participants with confirmed bilateral knee OA were enrolled. Inclusion criteria included a confirmed diagnosis of grade 2 or 3 knee OA based on the clinical classification criteria of the American College of Rheumatology, according to the radiographic evidence of Kellgren-Lawrence. All patients with a history of crystalline or neuropathic arthropathy, systemic or inflammatory joint disease, other intra-articular lesions, immunosuppression or acute infectious processes, coagulopathies, cancer or other tumor-like lesions, trauma, pregnancy or lactation, or any allergic reaction to, and receiving any treatments for knee OA in the previous 6 months were excluded from the study. The participants were asked to stop taking anti-inflammatory drugs and analgesics (except paracetamol) for at least three weeks before the intervention and during the study period. In this study, patients with mild to moderate stages of OA were enrolled (Figure 1).

Procedures and data gathering

To prepare the PRP, 48.5 mL of brachial vein blood was obtained via venipuncture and centrifuged at 2000 rpm for 5 minutes. The buffy coat and plasma-containing platelets were collected from the top of the sample and placed in a sterile tube, then centrifuged at 3000 rpm for 3 minutes. The double spin method was used to obtain PRP that was higher in leukocytes (14). Three-quarters of the plasma was collected and 0.2 mL of 8.4% sodium bicarbonate was added to the sterile tube. The platelet pellets were reconstituted with the remaining plasma in a 3 mL syringe, as reported by previous studies (15).

The steps of the main inclusion bilateral criteria of knee OA for all 34 patients were as follows: one knee was randomly allocated as the intervention (PRP injection) and the other knee was considered as the control. Two identical covered syringes, in aluminum foil and marked with the letters A and B, were provided to the physician; one contained PRP and the other was empty. The patients were positioned in a supine position and sterile drapes were placed in the surrounding area. An iodine solution was used to clean the patient's knee before the injection. After

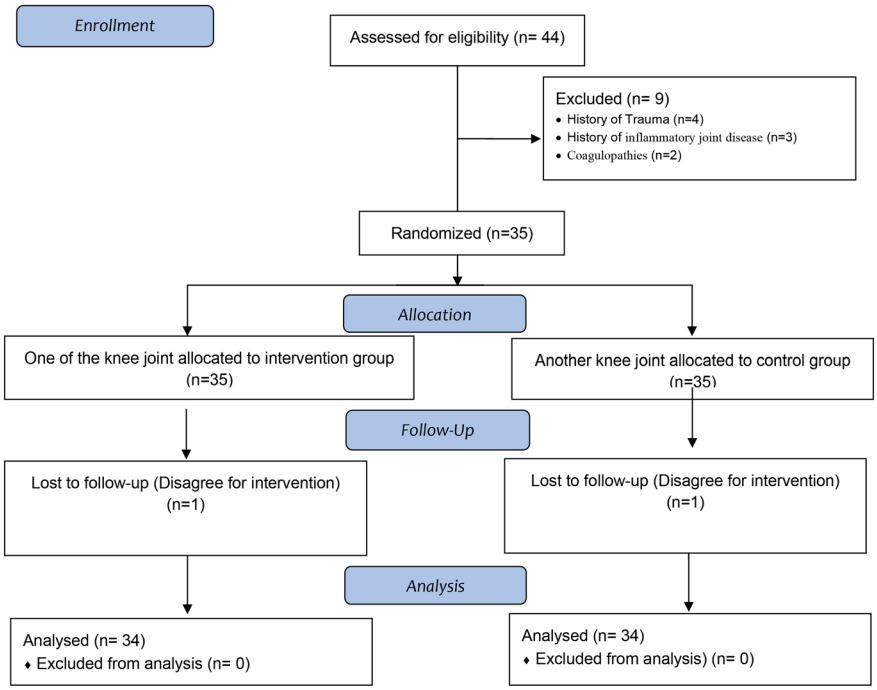

Figure 1. Flow diagram of enrollment and random assignment of study participants.

the injection, the patient remained resting in the supine position for approximately 20 minutes, during which passive extension and flexion of the knee were performed 15 times. An analgesic (paracetamol) was prescribed for the patients to be taken "as needed" in case of pain, and they were advised to limit their weight-bearing activities for at least 24 hours. Patients were followed up weekly after receiving PRP.

Before the intervention, baseline demographic data were recorded. Adverse events for the first month were recorded weekly and at third- and sixth-month assessment visits. Symptom severity was recorded for the first, third, and sixth months during the follow-up assessment visits using 100 mm EuroQol-visual analog scales (EQ-VAS). The EQ-VAS is a vertical visual analog scale that scores values from "0" (worst imaginable health) up to 100 (best imaginable condition). To document self-reported symptoms, patients completed the International Knee Documentation Committee (IKDC), the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the Tegner Activity Score (TAS). The IKDC is a purely subjective assessment that assigns patients a functional overall rating. Three categories are examined by the questionnaire: symptoms, athletic activity, and knee function. The symptoms subscale aids in evaluating issues like pain, stiffness, edema, and knee giving way. The stair climbing, standing up from a chair, squatting, and jumping functions are the emphasis of the sports activity subscale (16). The intraclass correlation coefficient (ICC), which varies from 0.87 to 0.98, was deemed sufficient (>0.70). Overall, it was discovered that the IKDC-SKF has positive test-retest reliability (17). The IKDC Subjective Form scored acceptably for construct validity (84% confirmation of the predefined hypotheses) and responsiveness (86% confirmation of the predefined hypotheses) (18). An ordinal scoring system is used to assign a score of 0 to responses that signify the lowest level of function or the highest level of symptoms for each item.

The response "Unable to perform any of the above activities due to knee pain" receives a score of 0, while the response "Very strenuous activities like jumping or pivoting as in basketball or soccer" receives a score of 4. This is how Item 1, which is related to the highest level of activity without significant pain, is scored. For Item 2, which asks about the frequency of pain in the last four weeks, the responses "Constant" and "Never" receive scores of 0 and 10, respectively. The IKDC Subjective Knee Evaluation Form is graded by adding the results of each item's scores and then converting the result to a scale from 0 to 100. Higher scores indicate higher levels of function and lower levels of symptoms, with the transformed score being regarded as a measure of function. If you have a score of 100, it means that you have no restrictions on your daily activities or athletic endeavors and don't experience any symptoms. The WOMAC Physical Function Subscale is a widely employed patient-reported measurement instrument for knee OA. The WOMAC has been used in other patient populations, including hip OA and rheumatoid arthritis (19).

The WOMAC comprises 24 questions covering the stiffness, pain, and physical functioning of the joint, and uses a five-point Likert scale for scoring (20). The Likert

method uses a five-point scale with the choices of none, mild, moderate, severe, or extreme, and the physical function subscale ranges from 0 to 68. The VAS method uses a 100mm horizontal line for each item and subjects mark a vertical line along the horizontal continuum for each item, which is measured and totaled with the other items on a scale of 0 to 1700.

For both scoring methods, higher scores represent more functional limitations (21). The TAS is a scale that aims to provide a standardized method of grading work and sporting activities. It is a graduated list of activities of daily living, recreation, and competitive sports. Patients are asked to select the level of participation that best describes their current level of activity and that before injury (22). A score of 0 represents sick leave or disability pension due to knee problems, whereas a score of 10 corresponds to participation in national and international elite competitive sports. A score of >6 can only be achieved if the person participates in recreational or competitive sports. The scale classifies work, recreational, and sports activities in a graded activity scale, using common terminology, so patients should not have difficulty selecting which level corresponds to their current activity. The degree of difficulty has been reported to increase with age (23). All surveys and functional tests were conducted at baseline and 3 and 6 months after the last administration, as symptoms improved in this timeframe based on previous studies (11,12).

Statistical analysis

Data were analyzed using paired t-tests, Wilcoxon tests, ANOVA for repeated measures, and Bonferroni multiple-comparison correction tests with SPSS 24.0 software. A significance level was considered less than 0.05.

Results

The mean (±SD) of age, body mass index, and symptom duration were 56.6 (10.2) years, 28.7 (4.7) kg/m^2, and 6.0 (4.3) years, respectively. 70.6% of patients were female. In terms of severity of disease, 67.6% (23) were in stage 2 and 32.4% in stage 3 of the disease. No treatment-related major adverse events were reported. All the patients completed the intervention period, and at one-month follow-up, most symptoms were resolved. The patients did not report any adverse effects during the administration and/or follow-up period. Mean ± standard error (18) of IKDC, WOMAC, TAS, and EQ-VAS scores in any assessing times in the PRP and control knees are presented in Table 1.

The mean of IKDC scores in knees that received PRP had increased 3 and 6 months after injection (F = 20.0 (2, 66), $P<0.001$, partial eta squared (η^2) = 0.378). So, the mean difference in IKDC score significantly increased 3 months (8.4, $P<0.001$) and 6 months (12.6, $P<0.001$) from baseline. In control knees, the mean of IKDC scores in assessing times showed a significant increase (F = 14.1 (2, 66), $P<0.001$, $\eta^2=0.299$). So, IKDC increased 3 (8.0, $P<0.001$) and 6 (11.2, $P<0.001$) months after the last injection in comparison to baseline was significant. The IKDC score before intervention was entered as a covariate in the analysis. In comparison between the groups, the use of the Bonferroni multiple comparison test indicated that 3 months ($P=0.899$) and 6 months ($P=0.669$) after intervention, the IKDC score in the intervention and control knees was not significant (Table 2). In addition, between-groups comparison indicated that the IKDC score significantly increased 6 months in comparison to 3 months (4.2, $P=0.048$) in PRP knees, but was not significant in the control knees ($P=0.133$).

Mean WOMAC scores in knees under PRP injection 3 and 6 months after injection showed significant improvement (F=14.6 (2, 66), $P<0.001$, $\eta^2=0.307$). The mean of WOMAC scores decreased significantly 3 months (6.1, $P=0.003$) and 6 months (8.6, $P<0.001$) after the last injection compared to before the injection. In the control knees, the mean of WOMAC scores showed significant improvement at assessing times (F = 8.2 (2, 66), $P=0.001$, $\eta^2=0.20$) and WOMAC scores significantly decreased at three (5.8, $P=0.009$) and six (6.9, $P=0.009$) months after the last injection in comparison to baseline.

Three months ($P=0.883$) and 6 months (p=0.504) after intervention, the WOMAC score in the intervention and control knees was not significant (Table 2). In addition, between-groups comparison indicated that WOMAC score in PRP knees ($P=0.072$), and control knees ($P=0.445$) at 6 months compared to three months after intervention was not significant.

Mean TAS scores in knees under PRP injection, 3 and 6 months after injection showed significant improvement (F=12.7 (2, 66), $P<0.001$, $\eta^2=0.277$). So, the mean of TAS scores significantly increased 6 months after the last

Table 1. Mean (standard error) for EQ-VAS, IKDC, WOMAC, and TAS at baseline and three and six months following final injection

	PRP (n = 34)			Control (n = 34)		
	Baseline	3 Months	6 Months	Baseline	3 Months	6 Months
EQ-VAS	65.6 (3.7)	72.9 (3.8)	77.1 (3.7)	65.3 (3.9)	72.9 (4.0)	77.1 (3.8)
IKDC	50.6 (2.7)	59.1 (2.6)	63.3 (2.9)	51.0 (2.2)	59.0 (2.3)	62.2 (2.8)
WOMAC	32.4 (3.1)	26.3 (2.5)	23.8 (2.4)	32.7(2.1)	26.9 (2.7)	25.8 (2.9)
TAS	58.6 (2.9)	61.5 (2.9)	70.0 (3.0)	57.6 (3.0)	61.0 (3.5)	67.3 (3.5)

Abbreviations: EQ-VAS, EuroQol-visual analog scales; IKDS, International Knee Documentation Committee; WOMAC, Western Ontario and McMaster Universities Arthritis Index; TAS, Tegner Activity Score.

Table 2. Adjust The adjusted difference between the two groups for EQ-VAS, IKDC, WOMAC, and TAS at three and six months following final the injection

	3 Months		6 Months	
	Mean difference (95% CI)	***P* value**	**Mean difference (95% CI)**	***P* value**
EQ-VAS	0.19 (-8.6 to 8.9)	0.966	0.11 (-9.7 to 10.0)	0.982
IKDC	0.33 (-4.8 to 5.5)	0.899	1.4 (-5.0 to 7.7)	0.669
WOMAC	0.34 (-4.3 to 5.0)	0.883	1.8 (-3.5 to 7.1)	0.504
TAS	0.32 (-6.3 to 6.9)	0.923	2.3 (-5.5 to 9.6)	0.592

Abbreviations: EQ-VAS, EuroQol-visual analog scales; IKDS, International Knee Documentation Committee; WOMAC, Western Ontario and McMaster Universities Arthritis Index; TAS, Tegner Activity Score; CI; confidence interval.

injection compared to baseline (11.4, $P=0.001$). In the control knees, the mean of TAS scores was significantly increased ($F=7.83$ (2, 66), $P=0.001$, $\eta^2=0.192$). So, TAS scores increased 6 months after the last injection (9.7, $P=0.005$) in comparison to baseline.

The TAS scores in the intervention and control knees were not significant three ($P=0.923$) and 6 months ($P=0.592$) after intervention (Table 2).

In addition, between-groups comparison indicated that the TAS score in PRP knees (8.5, $P<0.001$), and control knees (6.2, $P=0.002$) was significantly increased at 6 months compared to three months after intervention.

Mean the EQ-VAS scores in knees that received PRP injection, at 3 and 6 months after intervention showed significant improvement ($F=5.37$ (2, 66), $P=0.010$, $\eta^2=0.140$). Thus, the increase of the EQ-VAS scores only 6 months (11.5, $P=0.029$) after the intervention compared to baseline was significant. These results were seen in the control knees.

The EQ-VAS score in the intervention and control knees was not significant at three ($P=0.966$) and 6 months ($P=0.982$) after intervention (Table 2). In addition, between-groups comparison indicated that EQ-VAS score in intervention knees ($P=0.140$), and control knees ($P=0.147$) in the sixth month in comparison to the third month after intervention was not significant.

Discussion

We investigated the effect of the intraocular injections of PRP on the functional ability and symptoms in patients with mild to moderate knee OA. The findings showed a significant improvement in the knee that received PRP.

The results can be valuable and help to generalize the findings for other populations, due to conflicts reported in various populations, especially in Europe. Despite the small sample size in our study, the results were noticeable. The findings showed the effectiveness of intervention in knee OA without any adverse effects.

IKDC, WOMAC, TAS, and EQ-VAS scores in intervention knees and control, 3 and 6 months after intervention showed significant improvement.

The IKDC, WOMAC, TAS, and EQ-VAS scores in the intervention and control knees were not significant at 3 and 6 months after intervention ($P>0.05$). Comparison between groups indicated that the IKDC score significantly increased 6 months in comparison to three months later (4.2, $P=0.048$) in intervention knees, but not significantly in the control knees ($P=0.133$). However, the TAS score in intervention knees and control knees significantly increased at 6 months in comparison to three months after intervention. WOMAC and EQ-VAS score in intervention knees, and control knees at 6 months in comparison to three months after intervention was not significant.

A recent systematic review that included 14 RCTs concluded that PRP was likely to be more effective for pain relief and physical function when administrated as intra-articular injections (24). However, the present study, for the first time, investigates symptom severity, sports activity, lower limb function, and function in daily living activities. PRP contains some proteins that improve tissue repair and decrease inflammatory responses (25). Decreased inflammation and increased tissue repair may improve function and symptoms in patients Decreased inflammation and increased tissue repair may improve function and symptoms in patients with knee OA. The findings confirm the efficiency of the PRP as a novel agent for treatment approach in knee OA. In our study, those knees who received PRP did not report a significant improvement in symptom severity, sports activity, lower limb, and daily functions in comparison to control knees. It should be noted that the small sample size in pilot studies may reduce the statistical power and make it difficult to generalize the definitive result between groups. The absence of between-group differences in the pilot RCT might be partly attributed to a technique used for the preparation of the PRP. Dual spin centrifugation kits were used for the preparation of the PRP in this study that contained higher amounts of leukocytes compared to PRPs prepared by a single spin kit (26). Our findings agree with recent RCT results reported by other researchers who indicated improvements in self-reported symptom severity, sports activity and lower limb function following intra-articular injections of PRP produced using a leukocyte-rich method (27). In contrast, a recent meta-analysis has reported that leukocyte-poor PRP and leukocyte-rich PRP have similar safety profiles, but induce more transient reactions compared to hyaluronic acid. Adverse reactions for the PRP might not be directly

associated with leukocyte concentration (28). Cerza et al (29) indicated a significant improvement in overall WOMAC score at 12 and 24 weeks in patients with knee OA by administration of PRP prepared by a leukocyte-poor method compared to control cases. Our results and previous studies suggest that the leukocyte concentration in PRP can have a significant role in clinical outcomes in patients with knee OA.

Conclusion

Our findings suggest safety and feasibility data for the intra-articular administration of the PRP in patients with knee OA that may help to appraise a larger clinical trial. Findings show that PRP injection improves IKDC, WOMAC, TAS, and EQ-VAS scores, however, there was no significant difference with needling only (control knees). Parallel clinical trial studies with longer follow-up periods and larger sample sizes are recommended.

Limitations of the study

The most important limitation in this study was the effect of confounding factors, which according to the method and design tried to reduce this effect as much as possible by matching case and control groups.

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Authors' contribution

Conceptualization: Jamileh Moghimi.
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Formal analysis: Raheb Ghorbani.
Funding acquisition: Jamileh Moghimi.
Investigation: Hamid Reza Beiki.
Methodology: Raheb Ghorbani.
Resources: Hamid Reza Beiki.
Supervision: Jamileh Moghimi.
Validation: Raheb Ghorbani.
Visualization: Jamileh Moghimi.
Writing–original draft: Jamileh Moghimi and Hamid Reza Beiki.
Writing–review & editing: Jamileh Moghimi and Raheb Ghorbani.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Semnan University of Medical Sciences approved the study (Ethics committee reference number: 93/551664, 2015/1/13). Written informed consent was obtained from all participants before any intervention. This study was part of the internal medicine residential thesis of Hamid Reza Beyki at the university. The trial protocol was approved in the Iranian registry of clinical trials (Identifier: IRCT2015010112823N2; https://en.irct.ir/trial/12827) and Research Registry (Research Registry Unique Identifying Number: researchregistry9843).

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