

Comparison of Ultrasound Guided Intra- Articular Injection of Platelet Rich Plasma Versus High Molecular Weight Hyaluronic Acid in Improving Cartilage Thickness and Physical Functions in Patients with Primary Osteoarthritis of Knee: A Randomized Controlled Trial

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Abstract: ***Objective:** To compare ultrasound - guided intraarticular injection of platelet - rich plasma versus high molecular weight hyaluronic acid in improving cartilage thickness and physical functions in patients with primary osteoarthritis of knee. **Materials and Methods:** A randomized control trial conducted in the department of Physical Medicine and Rehabilitation, Regional Institute of Medical Sciences, Imphal, Manipur, India with sample size of 60 patients diagnosed with primary osteoarthritis of the knee, 60 patients were randomized to receive either ultrasound - guided single - dose intraarticular injection of platelet - rich plasma (study group) or high molecular weight hyaluronic acid (control group), Visual analog scale (VAS), Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and femoral condylar cartilage thickness by musculoskeletal ultrasound imaging. Follow up at 12 weeks, 24 weeks, and 36 weeks. **Results:** Both groups showed significant statistical improvement in VAS pain and WOMAC scores at 12, 24, and 36 weeks, but with no significant difference between the groups ($p>0.05$). VAS score in PRP group was 5.8 ± 0.924 at baseline and 1.8 ± 0.664 at 36 weeks. VAS score in hyaluronic acid group at baseline was 6.0 ± 0.946 and at 36 weeks was 2.0 ± 0.639 . WOMAC score in PRP group at baseline was 29.13 ± 11.77 and at 36 weeks was 13.6 ± 8.915 . In hyaluronic acid group WOMAC improved from baseline (29.53 ± 11.06) to 36 weeks (11.6 ± 6.284). There was no change in femoral condylar cartilage thickness in either group till 36 weeks follow - up. **Conclusions:** Single - dose intraarticular injection of platelet - rich plasma improves physical function in primary osteoarthritis knee but does not increase femoral condylar cartilage thickness. No additional benefits compared to a single - dose intraarticular high molecular weight hyaluronic acid injection.*

Keywords: Platelet - rich plasma (PRP), High molecular weight hyaluronic acid (HMWHA), Knee osteoarthritis, Femoral condylar cartilage thickness, Western Ontario and McMaster University Osteoarthritis Index (WOMAC),

1. Introduction

Osteoarthritis (OA) is a common degenerative joint disease characterized by articular cartilage erosion, osteophyte formation, and subchondral bone changes, particularly affecting the knee, shoulder, elbow, wrist, and ankle.^{1, 2} It predominantly affects older adults, leading to decreased ability to perform daily activities. Various factors, including female gender, obesity, family history, and joint trauma influence the condition.^{3, 4, 5} Knee OA is especially prevalent, with an estimated 10% to 15% of adults over 60 years affected, and is projected to rise significantly by 2050, potentially affecting over 130 million people globally.⁶

OA can be classified as primary or secondary, with both types sharing common pathological features. Pain and stiffness are the most prominent symptoms reported by individuals with knee OA, often worsening with activity. Physical examination reveals crepitus, bony enlargement, reduced range of motion, and joint instability. Radiographic evaluation plays a vital role in diagnosis.⁷

Current treatments, such as analgesics and anti - inflammatory medications, mainly provide symptomatic relief without significantly halting cartilage degeneration.⁸ Research is exploring innovative therapies like cytokine inhibitors, gene therapy, and platelet - rich plasma (PRP) to

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promote cartilage repair. PRP, an autologous concentration of platelets, contains growth factors that stimulate healing and may enhance chondrocyte metabolism and cartilage regeneration.⁸

While MRI offers a sensitive method for assessing cartilage thickness, its high - cost limits accessibility. Ultrasound is a more affordable and widely available technique that can directly measure cartilage thickness, providing valuable diagnostic insights and enabling monitoring of disease progression.^{9, 10}

This study aims to compare the efficacy of intraarticular PRP versus High molecular weight hyaluronic acid (HMWHA) in improving cartilage thickness and physical function in patients with primary knee osteoarthritis, addressing a gap in existing literature. Identifying effective treatment modalities is crucial for optimizing management strategies in OA.

2. Materials and Methods

The study was a randomized control trial conducted at the Department of Physical Medicine and Rehabilitation, RIMS, Imphal, Manipur, India, for a duration of 2 years commencing May 2022. Sample size was calculated 60 by taking into consideration the study conducted by Raеissadat SA et al¹⁷ with 90% power, 5% significance level. Inclusion criteria included age group 40 to 65 years, patients with primary knee osteoarthritis fulfilling 2016 ACR revised criteria for early diagnosis of knee OA, osteoarthritis of knee with Kellgren - Lawrence grade upto 1 to 3, willing to participate in the study and comply with treatment and follow up, Knee pain with VAS ≥ 4 . Exclusion criteria included recent knee trauma or knee surgery, knee deformity/knee infection, metabolic disease of bone, cognitive impairment, uncontrolled DM, thrombocytopenia (platelet count < 150000/mcl), intraarticular steroid injection during past 3 months, BMI > 30. All the participants were informed about the nature of the study, and those who agreed to participate were asked to sign the informed consent form. The approval of the Institutional Ethics Committee, RIMS, Imphal, was taken before starting the study. After getting informed consent, patients were allocated into two groups: Group 1=PRP group (30 patients) and Group 2=HMWHA group (30 patients) using a block randomization technique. PRP was prepared using double spin method: Whole blood was obtained by venipuncture in acid citrate dextrose (ACD) tubes. Centrifugation was done using a soft spin at 2400 rpm for 10 minutes, the supernatant plasma containing platelets was collected and centrifuge again at hard spin i. e. 3600 rpm for 15 minutes to obtain a platelet concentrate. The lower 1/3rd is PRP and upper 2/3 is platelet poor plasma (PPP). 4 ml of PRP was procured by removing the PPP.

Group 1 received ultrasound - guided intraarticular single - dose injection of 4 ml of PRP, and group 2 received ultrasound - guided intraarticular single - dose injection of high molecular weight hyaluronic acid (8mg) in the affected knee of interest. In addition to intraarticular injection, each case

received quadriceps and hamstring straightening exercises, and oral paracetamol was given as rescue drug. Patients were placed in supine position with affected knee slightly flexed and resting on a pillow. Proper aseptic measures was taken. After having located the patella, through a supero - lateral approach to the knee joint, under USG guided the needle was inserted along the superolateral margin of the patella.

Follow - up was done at the end of 12 weeks, 24 weeks, and 36 weeks. Patients of both groups received ice therapy for 10 minutes to the affected knee after the injection twice daily for 2 days. Paracetamol 650 mg tablet was given as rescue medication after injection. Knee care in activities of daily living and isometric strengthening exercises of quadriceps and hamstring for all the patients.

3. Outcome Measure

The treatment outcome was assessed with VAS for pain, WOMAC score and ultrasound assessment of medial, lateral and inter femoral condylar cartilage thickness. Using a 10 cm line, VAS for pain was assessed with two endpoints representing no pain and worst pain imaginable. The patient marks on the line the point that feel represents their perception of their current state. The VAS score is determined by measuring in centimeters from the left - hand end of the line to the point that the patient marks. WOMAC consists of three subscales: pain (5 items), stiffness (2 items), and physical function (17 items). Each item was measured in a five - point Likert scale, with a minimum WOMAC score of 0 and a maximum of 96. The individual is required to indicate the degree of difficulty, from 0 (none) to 4 (very strong), of pain and stiffness during the previous 72 hours. Femoral condylar cartilage thickness was measured by ultrasound. Cartilages of medial and lateral, and inter - trochanteric femoral condyles were examined with patients in a supine position under maximum flexion of their knee joints. Cartilage thickness was measured as the distance from a thin hyperechoic line at the synovial space - cartilage interface to a sharp hyperechoic line at the cartilage - bone interface.

4. Statistical Analysis

Data was collected in a pre - tested proforma and analysis was done using IBM - Statistical Package for the Social Sciences (IBM - SPSS) version 21. For descriptive statistics mean, frequency, percentage and standard deviation was used. Characteristics of the study participants for the continuous variables was analyzed by student's t - test. Characteristics of the study participants for categorical variables was analyzed by chi - square test. For comparison between the groups student's t - test was used. For within the group comparison repeated measure ANOVA was used. A p value < 0.05 was considered as statistically significant.

5. Results

There were 60 patients enrolled for the study. Data analysis was done for 60 patients.

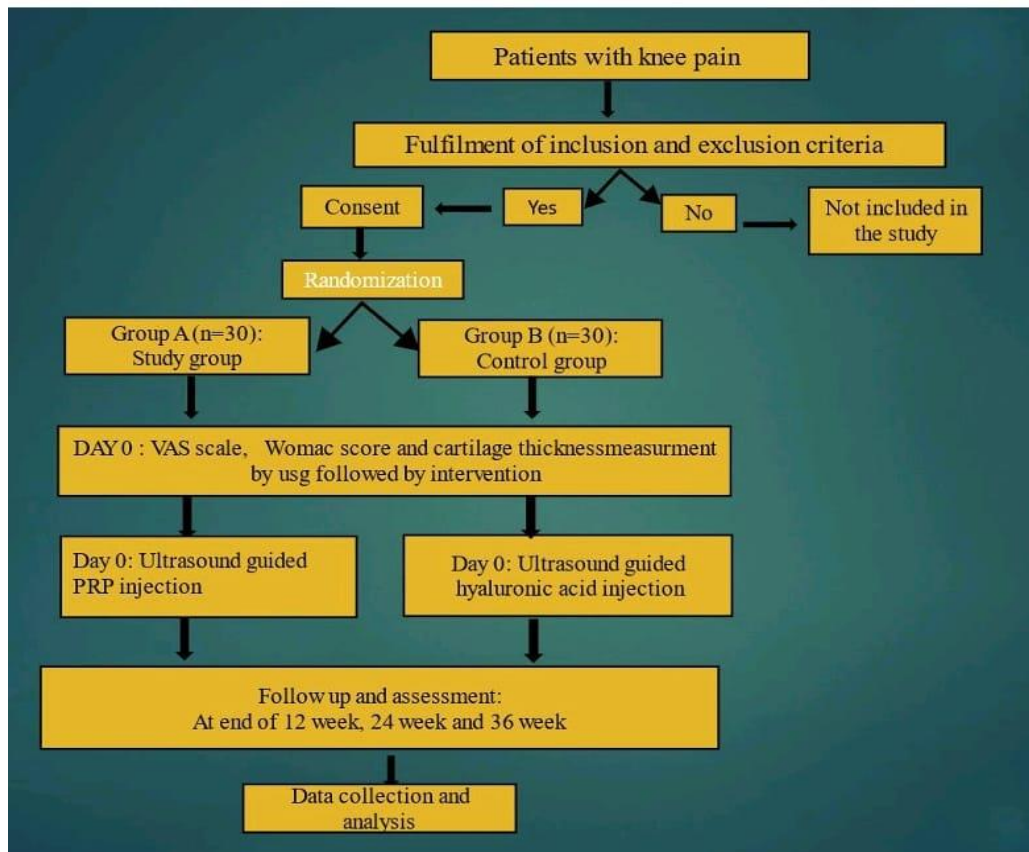


Figure 1: Flow diagram of the study design

Table 1: Comparison of baseline characteristics between study and control group (N=60)

Characteristics	Groups		P value
	Intraarticular PRP (n= 30) (n%)	Intraarticular HA (n= 30) (n%)	
Age in completed years (Mean ± SD)	57 ± 2.8	58 ± 2.5	0.543
Gender			
Male	6 (20%)	4 (13.3%)	0.731
Female	24 (80%)	26 (86.6%)	
Side of Affection			
Right	20 (66.6%)	16 (53.3%)	0.430
Left	10 (33.3%)	14 (46.6%)	
KL Grade			
1	4 (13.3%)	3 (10%)	0.274
2	18 (60%)	13 (43.3%)	
3	8 (26.6%)	14 (46.6%)	
BMI (Mean ± SD)	23.6 ± 81045	23.9 ± 1.13703	0.741
Occupation			
Homemaker	70%	66.6%	0.920
Farmer	10%	13.3%	
Shopkeeper	20%	20%	
Duration of Symptoms			
1 to 8 months	0%	6.6%	0.083
9 to 16 months	83.3%	56.6%	
17 to 24 months	16.6%	30%	
25 to 32 months	0%	6.6%	

Chi - square test, p - value < 0.05 taken as significant

The baseline characteristics of both groups were comparable, with no statistical difference.

Table 2: Comparison of baseline outcome measures between study and control group (N=60)

Outcome measures	Groups		Mean difference	95% CI of difference		P value
	Intraarticular PRP (Mean±SD)	Intraarticular HA (Mean±SD)		Lower	Upper	
VAS	5.8±0.924	6.0±0.946	-0.2	-0.6837	0.2837	0.411
Total WOMAC score	29.13±11.77	29.53±11.06	-0.4	-6.3049	5.50546	0.893
Cartilage thickness Medial condyle in mm	2.26±0.427	2.13±0.293	0.12667	-0.06286	0.31672	0.186
Cartilage thickness Lateral condyle in mm	2.27±0.450	2.19±0.305	0.07667	-0.12214	0.27606	0.443
Cartilage thickness Inter condyle in mm	2.41±0.428	2.45±0.424	-0.04	-0.26049	0.18049	0.718

T test, p value <0.05 taken as significant

No statistical significance for VAS pain score, WOMAC score, medial condylar cartilage thickness, lateral condylar cartilage thickness and inter condylar cartilage thickness.

Table 3: Comparison of outcome measures within the groups from baseline to 12 week, 24 weeks and 36 weeks

Parameter	Group	Baseline	12 weeks	24 weeks	36 weeks	P value
VAS pain score	PRP	5.8±0.924	3.7±0.827	2.7±0.773	1.8±0.664	0.02
	HA	6.0±0.946	4.2±0.714	3.0±0.556	2.0±0.639	0.01
WOMAC score	PRP	29.13±11.77	20.06±8.757	16.80±7.923	13.6±8.915	0.03
	HA	29.53±11.06	19.86±9.740	15.83±8.284	11.6±6.284	0.02
Medial condylar cartilage thickness in mm	PRP	2.26±0.427	2.26±0.427	2.26±0.427	2.26±0.426	0.102
	HA	2.13±0.293	2.14±0.292	2.17±0.295	2.17±0.289	0.101
Lateral condylar cartilage thickness in mm	PRP	2.27±0.450	2.27±0.450	2.27±0.450	2.27±0.450	0.2
	HA	2.19±0.305	2.20±0.304	2.20±0.317	2.22±0.328	0.102
Inter condylar cartilage thickness in mm	PRP	2.41±0.428	2.41±0.428	2.41±0.428	2.42±0.429	0.103
	HA	2.45±0.424	2.46±0.426	2.47±0.433	2.46±0.427	0.201

Repeated measures ANOVA

Statistically significant improvement in VAS score and in WOMAC score in both the groups, but there is no statistically significant changes in cartilage thickness in all follow - ups.

Table 4: Comparison of outcome measures between the two groups from baseline to 12 weeks, 24 weeks, and 36 weeks follow - up (N=60)

Parameter	Group	Baseline	P value	12 weeks	P value	24 weeks	P value	36 weeks	P value
VAS pain score	PRP	5.8±0.92	0.411	3.7±0.82	0.023	2.7±0.77	0.131	1.8±0.66	0.119
	HA	6.0±0.94		4.2±0.71		3.0±0.55		2.0±0.63	
WOMAC total score	PRP	29.1±11.77	0.893	20.06±8.75	0.934	16.8±7.92	0.646	13.6±8.9	0.319
	HA	29.5±11.06		19.86±9.74		15.83±8.28		11.6±6.3	
Medial condylar cartilage thickness in mm	PRP	2.2±0.427	0.18	2.2±0.427	0.177	2.2±0.427	0.216	2.2±0.426	0.195
	HA	2.1±0.293		2.1±0.292		2.1±0.295		2.1±0.289	
Lateral condylar cartilage thickness in mm	PRP	2.2±0.450	0.108	2.2±0.450	0.113	2.2±0.450	0.167	2.2±0.450	0.22
	HA	2.2±0.305		2.2±0.304		2.2±0.317		2.2±0.328	
Intercondylar cartilage thickness in mm	PRP	2.4±0.428	0.973	2.4±0.428	0.944	2.4±0.428	0.789	2.4±0.429	0.915
	HA	2.4±0.424		2.4±0.425		2.4±0.433		2.4±0.427	

Independent t test

Patients in PRP group showed statistically significant improvement in VAS score at 12 weeks follow up. But at 24 weeks and 36 weeks follow up, there was no significant difference between the two groups. There was no statistically significant difference in WOMAC score between the two groups in all follow - up. No statistically significant improvement was seen in femoral condylar cartilage thickness in both PRP and HMWHA groups in the 12 - week, 24 - week, and 36 - week follow - up periods.

6. Discussion

In the present study, the VAS pain score improved from baseline to 12, 24 and 36 weeks follow up in both the groups with a statistically significant improvement (p value<0.05). PRP group showed statistically significant difference with HMWHA group in VAS pain score at 12 weeks post - intervention. But at 24 and 36 weeks there was no statistically significant difference. The WOMAC score also showed

improvement from baseline to 12, 24 and 36 weeks follow - up in both groups; however, there were no statistically significant differences in mean changes from baseline to all follow up between the two groups.

Additionally, there were no significant changes in the thickness of medial femoral condylar cartilage, lateral femoral condylar cartilage, and intercondylar cartilage from baseline to follow - up in either group. In a study by Raeissadat SA et al¹¹ on platelet - rich plasma (PRP) versus hyaluronic acid (HA) injection for knee osteoarthritis, both PRP and HA were found effective. The primary outcome variables were VAS pain score, WOMAC score, and Lequesne index, with follow - up at 2, 6, and 12 months post - injection. The WOMAC score improved from baseline (41.96±11.71) to 12 months (27.10±12.3) in the PRP group, and from baseline (39.71±10.4) to 12 months (32.41±11.8) in the HA group, showing a statistically significant difference (p=0.02). Similarly, the VAS pain score improved in the PRP

group from baseline (7.8 ± 1.5) to 12 months (4.5 ± 1.7), and in the HA group from baseline (7.8 ± 1.1) to 12 months (6.1 ± 1.8), with a statistically significant difference ($p=0.0001$). Significant pain relief and functional improvement till 12 months in their study could probably be because of multiple PRP injections. Our study showed statistically significant improvements in WOMAC scores in both groups, but with no statistically significant difference between two groups.

A prospective interventional study by Johnson DS et al¹² examined the effects of intra-articular platelet-rich plasma (PRP) on cartilage thickness and clinical outcomes in knee osteoarthritis. They reported improvements in pain, joint stiffness, and activities of daily living, as well as in cartilage repair and regeneration. Clinical outcomes were assessed using VAS score and the knee osteoarthritis outcome score on 0, 90, and 180 days. Findings included a significant increase in cartilage thickness at middle trochlear notch (baseline: 2.43 ± 0.57 , day 180: 2.66 ± 0.54 , $p=0.002$) and medial femoral condylar (baseline: 0.8 ± 0.48 , day 180: 1.56 ± 0.38 , $p<0.0001$). These findings are not consistent with the present finding which observe no change in cartilage thickness at the end of 36 weeks. Johnson et al. administered three doses of 2 ml intra-articular PRP at seven-day intervals, while our study used a single 4 ml injection. Moreover, the significant cartilage thickness improvement which was reported by the study of Johnson et al. is contradictory with other studies showing cartilage regeneration which took place after one year follow up.¹⁸

Ekin I S et al¹³ studied the effects of platelet-rich plasma (PRP) on clinical outcomes and cartilage thickness in knee osteoarthritis patients, administering two intra-articular PRP injections (3 ml each) with a two-week interval. Outcome measures included VAS, WOMAC, Lequesne index, Short Form-36, and femoral cartilage thickness. Follow-up were conducted at one month, three months, and six months for all measures except femoral cartilage thickness, which was assessed via ultrasonography at baseline, three months, and six months. They reported medial femoral condylar cartilage thickness at baseline as 1.8 ± 0.2 and 1.9 ± 0.2 at six months ($p=0.108$), intercondylar thickness as 2.1 ± 0.2 and 2.2 ± 0.2 ($p=0.684$), and lateral condylar thickness as 1.9 ± 0.2 and 2.0 ± 0.2 ($p=0.063$). While intra-articular PRP improved pain, stiffness, physical function, and quality of life, it did not significantly affect cartilage thickness. These findings are consistent with our study in terms of VAS score, WOMAC score and no change in femoral condylar cartilage thickness.

Havva T Ç et al¹⁴ conducted a study to assess the efficacy of autologous platelet-rich plasma (PRP) in 82 patients (13 males, 69 females; mean age 63.5 ± 9.3 years) with advanced knee osteoarthritis. Participants received intra-articular PRP injections at the start and during the first two weeks of treatment. Clinical evaluations, including VAS, WOMAC, and the six-minute walk test, were conducted before treatment and at one, two, three, and six months. Ultrasound measured cartilage thickness before treatment and at three and six months. Results indicated significant reductions in VAS scores and improvements in WOMAC scores (both $p<0.001$) at three and six months, with the six-minute walk test also showing significant improvement ($p<0.05$). Cartilage thickness increased significantly compared to baseline

(0.6 ± 0.2 to 0.8 ± 0.2). These findings are contradictory to our findings as there was improvement in cartilage thickness in every 3 months and moreover baseline cartilage thickness was low in their study. Selection of patient groups (grade 3 and 4 OA) and MSK ultrasound techniques for cartilage thickness measurement was not comparable with the present finding as well as other contemporary literature.

A study by Park YB et al¹⁵ on the clinical efficacy of platelet-rich plasma (PRP) injections for mild to moderate knee osteoarthritis compared to hyaluronic acid (HA) found that PRP demonstrated better clinical efficacy. Outcome measures included the International Knee Documentation Committee subjective score, patient global assessment, VAS, and WOMAC. The follow-up periods were 6 weeks, 3 months, and 6 months post-injection. These results are in contrast to findings to present study, which showed improvement in both groups in VAS and WOMAC scores and PRP was not superior to HA in enhancing pain and function.

Ming LI et al¹⁶ conducted a study comparing intra-articular injections of platelet-rich plasma (PRP) and hyaluronic acid (HA) in patients with knee osteoarthritis. They found that while PRP significantly improved clinical outcomes after 6 months, it was not more effective than HA. The outcome measures included the International Knee Documentation Committee subjective score, Western Ontario and McMaster Universities score, and visual analogue scale (VAS). The follow-up periods were 1 and 6 months post-injection. This study aligns closely with our findings regarding VAS and WOMAC scores, despite differences in follow-up duration.

A study by Raeissadat SA et al¹⁷ compared platelet-rich plasma-derived growth factor to hyaluronic acid injections in individuals with knee osteoarthritis. The study reported significantly higher success rates in WOMAC total score and in VAS scale for the PRP group as compared to HA group at 12 months follow up (p value <0.05). These results are in contrast to present study, as they used 2 doses of PRP injections 3 weeks apart and they used triple centrifugation technique for PRP preparation.

This study comparing intraarticular PRP and hyaluronic acid found that both interventions improved pain, functional outcomes, and stiffness during all follow-up. Additionally, there was no significant changes in femoral condylar cartilage thickness compared to baseline. Other studies suggest that repeated PRP injections may have positive effect, indicating a need for further research to determine the ideal injection schedule for improving cartilage thickness in osteoarthritis of the knee. No serious complications were reported in either group post-procedure, with only mild erythema at the injection site, which resolved on its own.

7. Limitations of Study

Some of the limitations of the study were its short duration follow up and small sample size. The potential long-term benefits of PRP were not assessed. Subgroup analysis of different grades of OA knee were not considered in the present study.

8. Conclusion

The study shows that ultrasound guided intraarticular platelet rich plasma injection is effective in improving pain and physical functions in patients with primary osteoarthritis knee. PRP shows no effectiveness in improving femoral condylar cartilage thickness. The study also shows that there is no added benefits in treatment with single dose intraarticular platelet rich plasma injection in primary osteoarthritis knee patients while comparing to single dose intraarticular high molecular weight hyaluronic acid injection. However, further studies with larger sample sizes, longer follow - up periods, and a proper dosing schedule of injections are necessary to find out if there is any regenerative potential of PRP on femoral articular cartilage.

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Ethical approval

The study was approved by the Institutional Ethics Committee RIMS Imphal

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