Original Article

Beneficial effects of platelet-rich plasma on improvement of pain severity and physical disability in patients with plantar fasciitis: A randomized trial

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Abstract

Background: The present study aimed to clinically examine the effects of platelet-rich plasma (PRP) on improvement of plantar fasciitis and its related manifestations.

Patients and Methods: This single-blind randomized controlled trial was performed on 32 consecutive patients with the final diagnosis of plantar fasciitis that were randomly assigned to the case group (that received PRP, $n = 16$) and the control group (that received corticosteroid as methylprednisolone 1 ml plus lidocaine 1 ml, $n = 16$). The endpoints in the present study were changes in the visual analog scale score and the modified Roles and Maudsley score (RMS) from baseline, 1-month, 3 months, and 6 months follow-up. Plantar fascia was also assessed by B-mode sonography before and also 3 months after primary assessment.

Results: Regarding the pain severity, the PRP group had significantly higher mean pain score at 3 time points of before injection, as well as 1 and 3 months after PRP use when compared to the corticosteroid group ($P < 0.05$); however, the control group experienced significantly higher pain severity than the PRP group at 6 months after interventions. Also, RMS was lower in PRP group than in corticosteroid group at baseline as well as at 1 and 3 months after injections ($P < 0.05$). In sonography assessment, no difference was revealed.

Conclusion: Administration of PRP leads to significant improvement in pain severity and physical limitation in patients with plantar fasciitis. This healing effect may be begun at least 3 months after injection.

Key Words: Ability, corticosteroid, pain, plantar fasciitis, platelet-rich plasma

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INTRODUCTION

Plantar fasciitis is frequently manifested by a long-term, but self-limited pain on the plantar region of the foot and inferiorly in the heel that is, commonly revealed in adults limiting their activities due to severe pain and leading physical disability.[1] Similar to most inflammatory-based disorders, plantar fasciitis has more intensity in early morning as well as after a long time physical inactivity that can be notably lowered following weight reducing.[2] In more deteriorated conditions, it can be also accompanied with nocturnal pain and paresthesia.[3] Physically, the pain of plantar fasciitis can be severed by dorsiflexion of the foot and also with the extension of the knee.[4] It seems that acute or chronic injury to plantar fascia because

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of chronic overload physical stresses is the main pathophysiological fundament of the disease.[5] Despite considering various diagnostic modalities, plantar fasciitis is certainly diagnosed on medical history and physical examination.[6] On the other hand, imaging may not be helpful to diagnose the disease and only can be limitedly applied to differentiate it from other pathological conditions.[7] Along with diagnostic approaches, various treatment modalities have been also examined to treat plantar fasciitis including medications using anti-inflammatory drugs and corticosteroids, and no-drug approaches such as taping, shoe inserts, posterior-tension night splints, stretching protocols, extracorporeal shock wave therapy, and even surgery.[8-10] However, applying these options have been associated with a wide spectrum of treatment responses or provide short-term benefits.[11] Some treatment approaches even lead to plantar fascia rupture.[12]

Platelet-rich plasma (PRP) is plasma enriched with platelets stimulating bone and muscle healing. The PRP is frequently used for tissue repair mediated by different types of cytokines and growth factors.[13] Clinically, PRP is widely used to heal tendinitis, neural injuries, cardiac muscular injuries, osteoarthritis, oral surgery, and plastic surgery.[14,15] It is also used as a beneficial treating modality in sport medicine to rehabilitate disable muscles.[16] However, all of these approaches were resulted in inconsistent treatment response rates in different clinical trials.

Recently, the use of PRP has been tested in comparison with other treatment options and medications for treatment of plantar fasciitis. In some trials, using PRP was associated with more improvement in activity limitation and physical disability when compared with corticosteroids and even with surgical management.[17,18] However, the beneficial effects of PRP remained already uncertain and needs to more assessment. Hence, the present study aimed to clinically examine the effects of PRP on improvement of plantar fasciitis and its related manifestations.

PATIENTS AND METHODS

Study population

This randomized single-blind was performed on 32 consecutive patients with the final diagnosis of plantar fasciitis who referred to physical medicine clinics of Isfahan University of Medical Sciences in 2014. The inclusion criteria were age >18 years, chronic plantar fasciitis (duration more than 3 months), and lack of effect of conservative treatment. The exclusion criteria included history of receiving corticosteroids within the last 6 weeks, history of surgical interventions in the ankle and the heel, receiving aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) within a week ago, history of stroke within the last 3 months, pregnancy or breast feeding, malignancy, anemia, diabetes mellitus, hypothyroidism, peripheral neuropathy, acute infection or fever, and coagulopathies.

The study protocol was approved by the Research and Ethics Committee at the University and written informed consent was received from all study subjects.

Randomization

The computer-generated randomization sequence was used to allocate participants into 1:1 ratio in both the arms. It was assumed that participants would be distributed approximately equally by gender and age in both intervention and control arms.

Study protocol

The study protocol is demonstrated in Figure 1. The referred patients were initially examined by a single physiatrist and those with the tenderness at the junction of fascia to calcaneus at the medial plantar were primarily diagnosed as plantar fasciitis. The included patients were then randomly assigned to the case group (that received PRP, n = 16) and the control group (that received corticosteroid as

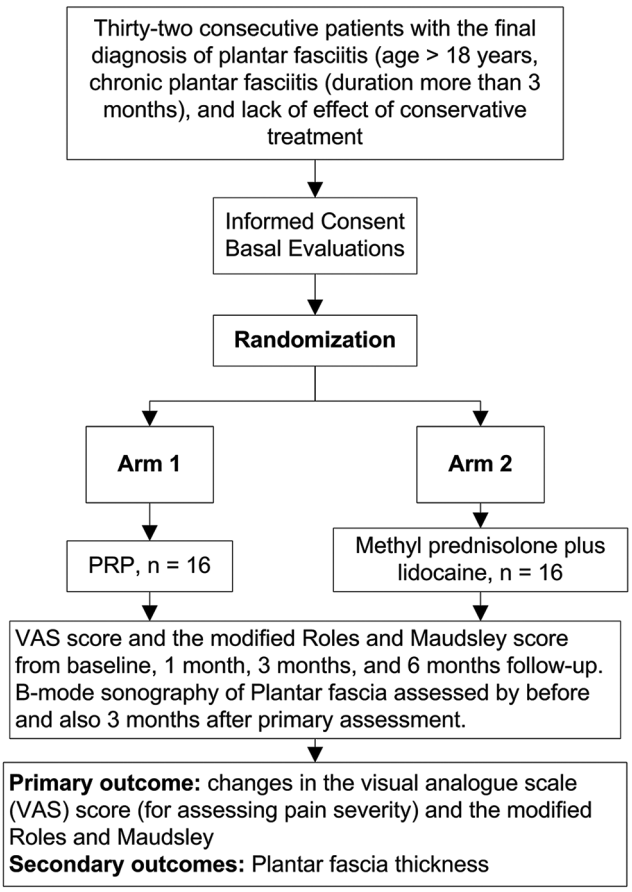

Figure 1: Participants flowchart

methylprednisolone 1 ml plus lidocaine 1 ml, n = 16). PRP preparation was carried out by adapting the protocol proposed by Sonnleitner *et al*.[19] The 40 ml collected intravenous blood was firstly centrifuged at 1600 rpm, for 12 min, at environmental temperature. After isolating erythrocytes, the serum containing platelets and white blood cells (as poor platelet plasma) were centrifuged at 3500 rpm, for 12 min for achieving 3 ml of PRP. After preparing PRP, it was placed inside the ice and injected into the targeted point of the cases within a maximum of 1 h. For testing the efficacy of the prepared PRP, cell blood count was taken from the patients before and also after PRP injection that checking the level of serum PRP platelet should expected at least 6-fold increase in platelet levels than before the PRP injection. All injections (for PRP and corticosteroids) were done by the physical therapist at supine position and in neutral position of the ankle. Afterward, the maximal point of the tenderness was found and injection was performed with the medical approach. After injection, ice was placed at the injection site for 15 min and repeated for 4–5 times in the day of injection. In the event of local pain, the patients were recommended to elevate the lower extremity. The patients were educated to schedule the program of stretching the achilles tendon and plantar fascia. Also, they were asked not to use corticosteroids or NSAIDS and only used acetaminophen if severe pain appeared.

It is significant that the patient and the physician were not blind to the study, and only the data collector was blind to the treatment group. The data were collected by a physical therapist that was trained for the measurements.

Study measurements

The endpoints in the present study were changes in the visual analogue scale (VAS) score (for assessing pain severity) and the modified Roles and Maudsley score (RMS) (for assessing pain and limitation of activity) from baseline to 6 months follow-up. All patients completed a VAS in which 0 was no pain and 10 the worst imaginable pain, before injections and also 1, 3, 6 months after injections. The VAS score was determined in the early morning, the mean total day, and after a 10-step walking. Modified RMS were also completed at the same time points. This scoring system is a subjective 4-point patient assessment of pain and limitations of activity (1 = excellent result with no symptoms following treatment; 2 = significant improvement from pretreatment; 3 = patient somewhat improved; 4 = poor, symptoms identical or worse than pretreatment). Plantar fascia was also assessed by B-mode sonography before and also 3 months after primary assessment to determine the thickness of the plantar fascia, calcification, echogenicity, and biconvexity parameters.

Statistical analysis

Results were presented as mean ± standard deviation for quantitative variables and were summarized by frequency (%) for categorical variables. Continuous variables were compared using t-test nonparametric Mann–Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using Chi-square test. Change in study parameters was assessed using paired t-test or McNemar test. The trend of the changes in study parameters was assessed using the repeated measure ANOVA test. For the statistical analysis, the statistical software SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA) was used. P = 0.05 or less was considered as statistically significant.

RESULTS

The two groups received PRP or corticosteroid were similar in terms of some baseline characteristics such as gender distribution, mean age, mean disease duration, mean height and side of involvement, but the average weight was significantly higher in PRP group [Table 1].

Regarding mean pain severity (VAS score), the PRP group had significantly higher mean pain score (in the early morning, the mean total day, and after a 10-step walking) at 3 time points of before injection, as well as 1 and 3 months after PRP use when compared to the corticosteroid group; however, the control group experienced significantly higher pain severity than the PRP group at 6 months after interventions [Table 2]. At baseline, no difference was observed in RMS between PRP and corticosteroid groups, while 1 and 3 months after initial interventions, corticosteroid group experienced higher physical ability than PRP group; however, this superiority was adversely changed

Table 1: Baseline characteristics in PRP and corticosteroid groups

Characteristics	PRP group (n=16)	Corticosteroid group (n=16)	P
Male gender (%)	4 (25.0)	5 (31.2)	0.99
Age (year) ± SD	45.44±7.74	47.12±10.70	0.61
Disease duration (month) ± SD	27.56±30.92	29.84±29.35	0.83
Height (cm) ± SD	165.19±7.51	164.88±9.87	0.92
Weight (kg) ± SD	86.03±11.82	75.13±12.11	0.02
Side of involvement (%)			
Right	10 (62.5)	10 (62.5)	1.000
Left	6 (37.5)	6 (37.5)	

SD: Standard deviation, PRP: Platelet-rich plasma

Table 2: Changes in mean pain severity score in 4 time periods in early morning, after walking, total day and RMS

Item	Before injection	1-month later	3 months later	6 months later	*P*
VAS (total day)					
PRP group ± SD	8.50±0.97	5.50±1.86	3.50±1.63	1.50±1.97	<0.001
Steroid group ± SD	7.12±1.78	3.19±1.80	2.00±2.10	4.81±2.66	<0.001
P	0.012	0.001	0.031	<0.001	0.327
VAS (early morning)					
PRP group ± SD	9.31±0.70	6.12±2.06	3.88±1.59	1.75±1.95	<0.001
Steroid group ± SD	7.31±2.87	3.69±1.92	2.31±2.36	5.81±2.48	<0.001
P	0.011	0.002	0.036	<0.001	0.305
VAS (after walking)					
PRP group ± SD	8.25±1.13	5.12±1.86	2.94±1.44	1.12±2.03	<0.001
Steroid group ± SD	6.88±1.78	3.00±1.93	2.06±2.27	5.06±2.54	<0.001
P	0.014	0.003	0.040	<0.001	0.807
RMS					
PRP group ± SD	1.00±0.00	2.00±0.82	2.62±0.81	3.62±0.89	<0.001
Steroid group ± SD	1.25±0.68	3.00±0.97	3.50±0.73	2.06±1.06	<0.001
P	0.154	0.004	0.003	<0.001	0.369

SD: Standard deviation, VAS: Visual analogue scale, RMS: Roles and Maudsley score, PRP: Platelet-rich plasma

after 6 months of intervention indicating higher physical ability in PRP group than in corticosteroid group, 6 months after injection [Table 3]. On the other hand, at baseline, 100% of patients in PRP group and 87.5% in control group had poor physical ability, but after 6 months of initial assessment, 81.2% in PRP group and only 6.2% in control group experienced excellent physical ability based on the RMS system ($P < 0.001$) [Table 4].

In sonography assessment, the mean plantar fascia thickness at baseline was 3.66 ± 1.31 mm in PRP group and 3.16 ± 1.05 mm in corticosteroid group with no difference ($P = 0.243$). At 3 months after drug injections, although mean plantar fascia thickness was considerably reduced in both groups, this index was not different between the two groups 3 months after interventions (1.93 ± 0.46 mm vs. 2.08 ± 0.65 mm, $P = 0.454$) [Figure 2]. With respect to echogenicity, at baseline, normal echogenicity was revealed in 6.2% of patients in PRP group and 37.5% of cases in control group, while hypo-echogenic pattern was found in 81.2% and 43.8% and hyper-echogenic pattern in 12.5% and 18.8%, respectively ($P = 0.062$). After 3 months of drug injections, normal echogenicity was found in 81.2% and 93.8%, hypo-echogenic pattern in 18.8% and 0.0%, and hyper-echogenic pattern in 0.0% and 6.2%, respectively ($P = 0.126$). At baseline, positive biconvexity was identified in 56.2% of patients in PRP group and 31.2% of those in steroid group with no difference ($P = 0.154$), while positive biconvexity was found in none of the patients in both PRP and control groups. In addition, calcification was not revealed in both study groups at baseline and also at 3 months after interventions.

Table 3: Changes in RMS in 4 time periods

Item	Before injection (%)	1-month later (%)	3 months later (%)	6 months later (%)
RMS* (PRP group)				
A	0 (0.0)	5 (31.2)	4 (25.0)	1 (6.2)
E	0 (0.0)	0 (0.0)	3 (18.8)	13 (81.2)
G	0 (0.0)	6 (37.5)	3 (18.8)	1 (6.2)
P	16 (100)	5 (31.2)	0 (0.0)	1 (6.2)
RMS (steroid group)				
A	2 (12.5)	2 (12.5)	4 (25.0)	6 (37.5)
E	0 (0.0)	7 (43.8)	10 (62.5)	1 (6.2)
G	0 (0.0)	7 (43.8)	2 (12.5)	2 (12.5)
P	14 (87.5)	0 (0.0)	0 (0.0)	7 (43.8)
P	0.144	0.004	0.016	<0.001

*RMS: Roles and Maudsley score, PRP: Platelet-rich plasma

Table 4: The physical ability status based on RMS in PRP and control groups in 4 time periods

Item	Before injection (%)	1-month later (%)	3 months later (%)	6 months later (%)
PRP group				
Poor	16 (100)	5 (31.2)	0 (0.0)	1 (6.2)
Good	0 (0.0)	6 (37.5)	9 (56.2)	1 (6.2)
Acceptable	0 (0.0)	5 (31.2)	4 (25.0)	1 (6.2)
Excellent	0 (0.0)	0 (0.0)	3 (18.8)	13 (81.2)
Steroid group				
Poor	14 (87.5)	0 (0.0)	0 (0.0)	7 (43.8)
Good	0 (0.0)	7 (43.8)	2 (12.5)	2 (12.8)
Acceptable	2 (12.5)	2 (12.5)	4 (25.0)	6 (37.5)
Excellent	0 (0.0)	7 (43.8)	10 (62.5)	1 (6.2)
P	0.144	0.004	0.016	<0.001

RMS: Roles and Maudsley score, PRP: Platelet-rich plasma

Regarding trend of the changes in pain severity, this trend was statistically significant in both PRP group and steroid group, but with the different pattern that the mean VAS score was gradually decreased in

PRP group within a 6 months follow-up time, while in control group, this trend was downward within 3 months after steroid use, but was increased during 3 months after that [Figure 3]. Also, regarding trend of the changes in the RMS, this ability score was gradually increased in PRP group within 6 months follow-up time, but this trend had an inconsistent trend with an increasing pattern within first 3 months after steroid injection, but with a decreasing trend 3 months after that [Figure 4].

DISCUSSION

Reviewing the literature with regard to the beneficial role of PRP on healing different types of plantar fasciopathies achieves limited clinical trials with contradictory results. Some current evidences for using PRP in plantar fasciitis have indicated promising results and presented this method as a safe option,[20] but some others could not clearly confirm the potential role of PRP in healing plantar fasciitis.[21] However, similar to our observation, most recent studies could show its high efficacy to improve disease-related pain and disability a short time after injection. In a study by Shetty *et al*.[22] and using two American Foot and Ankle Score (AFAS) and Foot and Ankle Disability Index, significant improvement in pain and disability was obtained 3 months after administration. In a report by O'Malley *et al*. (done),[23] improvement in pain, physical ability, and also health-related quality of life were observed about 3 months after the last PRP injection. Comparing the effects of corticosteroid and PRP also showed more effectiveness and durability in PRP group for treating plantar fasciitis.[17] One of the interesting results in our trial is that the use of corticosteroid led to quick but short-term effect of corticosteroid when compared with PRP; however, our study showed beginning considerable effect of the PRP after 3 months of administration. Furthermore, beneficial accelerative effects of PRP can be expected about 3 months after injection, but consistent effect may not be observed following use of corticosteroid.

Regarding trend of the effects of PRP and corticosteroid on pain severity and physical ability, our study could show early effects of corticosteroid, but delayed beneficial effects of PRP. On the other hand, our study showed an increasing trend of physical ability as well as decreasing trend of pain severity during 6 months after PRP injection, but beneficial effects of corticosteroid on pain and physical ability was only observed within 3 months after injection. The difference in the trend of the changes in pain and disability between PRP and steroids was also previously observed. In a study by Say *et al*. and using VAS score and the AFAS, although mean AFAS was higher in PRP group than in steroid group, this score was significantly lower in PRP group at 6 months intervention. Similar trends were revealed

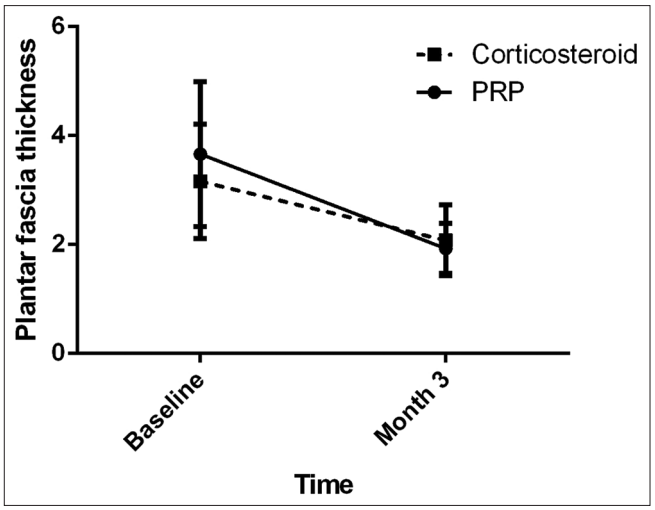

Figure 2: plantar fascia thickness in baseline and month 3

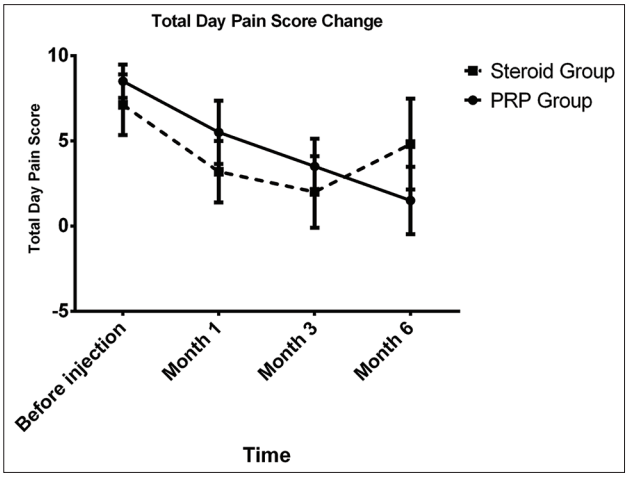

Figure 3: Trend of the changes in total day pain score in platelet-rich plasma and steroid group

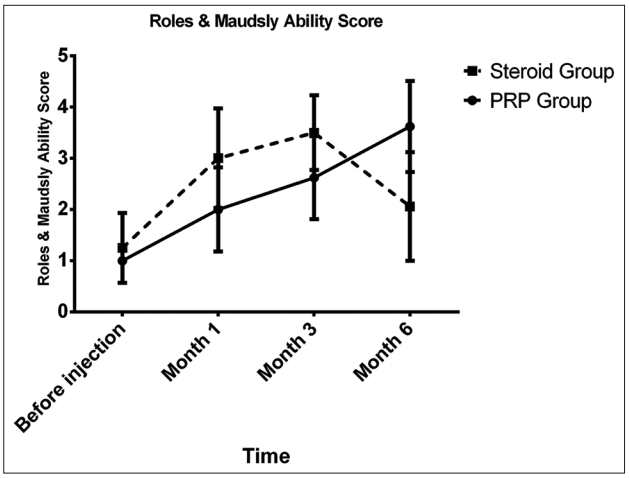

Figure 4: Trend of the changes in Roles and Maudsley ability score in platelet-rich plasma and steroid group

in another study by Monto[17] that the corticosteroid group had a pretreatment average the American Orthopedic Foot and Ankle Society (AOFAS) hind-foot score of 52, which initially improved to 81 at 3 months posttreatment but decreased to 74 at 6 months, then dropped to near baseline levels of 58 at 12 months, and continued to decline to a final score of 56 at 24 months. In contrast, the PRP group started with an average pretreatment AOFAS score of 37, which increased to 95 at 3 months, remained elevated at 94 at 6 and 12 months, and had a final score of 92 at 24 months. Most studies aimed to assess the effects of PRP as a single interventional group without control group and some others considered a short-term follow-up time shorter than 6 months and thus the observed trend in our study could not be reveal in most similar studies.

The effect of PRP on healing plantar fasciitis is mainly related to some growth factors and cytokines. The PRP is enriched by platelet-derived growth factor, endothelial growth factor and transforming growth factor as well as some anti-inflammatory and pro-inflammatory cytokines interleukins including interleukins 4, 8, 13, 17, tumor necrosis factor-α and interferon-α.[24] The combination of these growth and anti-inflammatory components can initiate the healing stages necessary to reverse the degenerative process at the base of the plantar fascia, enhance fibroblast migration and proliferation, up-regulate vascularization and also can increase collagen production and deposition.[25] However, these influences seem to be dose-dependent and thus obtaining optimal dosage with maximized effect is necessary.

In the present study, beside comparing effects of PRP in comparison with corticosteroids on clinical improvement in patients with plantar fasciitis using clinical scores, some sonographic parameters including the thickness of the plantar fascia, calcification, echogenicity, and biconvexity parameters were also assessed. Although plantar fascia thickness, echogenicity, and positive biconvexity were all improved within follow-up time in both groups receiving PRP and corticosteroid groups, no difference was found across the two groups. In total, it seems that along with clinical scoring systems, using these ultrasonography parameters can be helpful to assess improvement of pain and disability in patients who treated with treatment regiments such as PRP in patients with plantar fasciitis.

In this study, the volume of methylprednisolone and PRP was not the same which could have some effects on the reduction of pain that was the main limitation of this study.

CONCLUSION

The injection of PRP results in significant improvement in pain severity and physical ability in patients with plantar fasciitis. This beneficial effect is appeared about 3 months after injection of PRP, but can be continued consistently for longer time when compared with corticosteroid. Because of this long-term effect of PRP, its use is more preferred than corticosteroid in plantar fasciitis.

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Conflicts of interest
There are no conflicts of interest.

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