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Original Article

Bone graft plus platelet-rich plasma affects fracture healing and elbow joint recovery of patients with humeral condylar bone defect

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Abstract: Objective: This paper was aimed at exploring the effects of bone graft (BD) combined with platelet-rich plasma (PRP) on the fracture healing and the functional recovery of the elbow joint of patients with humeral condylar bone defect (HCBD). Methods: 184 HCBD patients treated with autogenous bone graft (ABG) in our hospital from February 2018 to July 2019, were enrolled and divided into two groups. Those treated with BG combined with PRP were in a joint group (n = 101), and those treated with traditional surgery were in a control group (n = 83). The two groups were compared in terms of surgical indicators. The Visual Analogue Scale (VAS) and the Mayo Elbow Performance Score (MEPS) were used to assess the patients' pain severity and elbow functions before treatment, and one month and three months after treatment. Before and after treatment, the expression of inflammatory cytokines was observed. The patients were observed and recorded for their postoperative adverse reactions. Their recovery was also measured and recorded. The Activity of Daily Living Scale (ADL) was used to evaluate their postoperative quality of life (QOL). Results: After treatment, the surgical indicators in the joint group were significantly better than those in the control group, and the expression of the cytokines was significantly lower in the joint group. One month and three months after treatment, the VAS scores were significantly lower, while the MEPS scores were significantly higher in the joint group. After treatment, compared with those in the control group, patients in the joint group had a significantly lower total incidence of complications, significantly better recovery, and significantly higher ADL scores. Conclusion: For HCBD patients undergoing ABG, PRP can accelerate fracture healing, relieve pain, and improve the functions of the elbow joint.

Keywords: Bone graft combined with platelet-rich plasma, humeral condylar bone defect, fracture healing, elbow joint functions

Introduction

Humeral condylar fractures are one of the most common fractures among young people, for whom the rapid functional recovery of the elbow joint is particularly important [1, 2]. The elbow joint is prone to comminuted fractures because of its complex anatomical structure, but there are difficulties in its effective restoration and fixation [3]. Due to the improper selection of fixation, most patients suffer from bone resorption, defects, and nonunion, which seriously affect the functions of the elbow joint [4]. Clinically, humeral condylar bone defect (HCBD) is mostly treated by scavenging infection foci, repairing soft tissues, and rebuilding bone continuity. However, in order to avoid more serious bone defects, the foci are not scavenged completely and accurately during therapeutic processes, which thus increases the risk of recurrence of infection [5-7]. Therefore, it is essential for treating HCBD to find safer and more effective methods.

Autogenous bone graft (ABG) that has a high healing rate is the most widely used method to treat bone defects at present [8]. After undergoing ABG, patients have relatively long bony union time (BUT), which leads to the delayed time to start functional exercises and affects the postoperative functional recovery of the elbow joint [9]. Therefore, in this study, platelet-rich plasma (PRP) combined with ABG was used to treat HCBD. As an autologous whole blood product, PRP provides platelets with super-physiological concentrations, growth fac-

tors, leukocytes, and other bioactive proteins, which can be delivered to injured sites [10]. Recently, this product is clinically regarded as a biological adjunctive therapy, because it can repair intra-articular hyaluronic acids, increase the synthesis of glycosaminoglycans in chondrocytes, and balance articular angiogenesis, as well as provide a stent for the migration of stem cells [11]. For instance, this therapy repairs rotator cuff tears under arthroscopy, reduces the recurrence rate of the disease, and improves patients' shoulder function [12]. For patients with bone defects, PRP combined with bone grafting (BG) can shorten the time of fracture healing and reduce the occurrence of complications [13].

In this study, PRP was given to HCBD patients undergoing ABG, in order to explore its influences on the fracture healing, the functional recovery of the elbow joint, and the quality of life (QOL) of the patients, further providing a feasible therapeutic scheme for them.

Materials and methods

General information

One hundred and eighty-four HCBD patients treated with ABG in Chongqing University Three Gorges Hospital from February 2018 to July 2019, were enrolled and divided into two groups based on different therapeutic methods. Those treated with BG combined with PRP were in the joint group (n = 101), and those treated with traditional surgery were in the control group (n = 83). Inclusion criteria: All patients who were confirmed with HCBD by CT or X-rays [14]; patients with complete clinical data; patients who were unhealed within one year after fracture, those with bone resorption at the fracture end; patients who needed to be treated with ABG; patients with bone defects at a single site. This study was approved by the Ethics Committee of our hospital. The research objects and their families were informed and they signed a fully informed consent form. Exclusion criteria: Those complicated with inflammatory lesions and open wounds, or joint deformities and rheumatoid arthritis; those with coagulation disorders, inflammatory diseases of the blood system, or cognitive impairment; those accompanied by mental illness or a family history of mental illness; those withdrawing from the experiment halfway; those who did not cooperate in this study; those who were lost to follow up.

Preparation and surgical methods of PRP

Preparation of autologous PRP: Half an hour before operation, 200 mL of venous blood was extracted from the patients for shaking evenly. Next, autologous PRP was prepared by twice centrifugation, and then centrifuged at 1500 × g (4°C, 10 minutes) in a centrifuge to separate red blood cells. After that, the plasma was centrifuged at 1500 × g (4°C, 10 minutes) in a centrifuge again. Platelet concentrates were in the lower layer, and platelet-poor plasma was in the supernatant, with approximately 6-8 mL of autologous PRP obtained. Finally, the autologous PRP was shaken on a shaker to prevent platelet coagulation.

Iliac bone graft

All patients were given general or nerve blocking anesthesia. The fracture was exposed from the original surgical approach, and internal fixation should be taken out first from those with the fixation. After the humeral condyle was exposed, the inactivated sequestra and scar tissues were thoroughly cleaned, and the hardened bones and redundant calluses were removed to expose fresh cancellous bones. The free fibrous tissues and bone blocks on the articular surface were cleaned, while avoiding damage to the original articular cartilage. Based on the defected bones in the condyle, the fracture end was restored, and then the iliac bone cut from the crista iliaca was put into gentamicin saline for later use. For those in the control group, the prepared iliac bone for autogenous graft was implanted into the fixed defect, while for those in the joint group, the PRP and the graft bone were implanted. Then, the removed autogenous iliac bone was immersed. During the BG, the bone that was mixed with the autologous PRP was implanted, and other centrifuged blood components were input into the patients. According to the defects in lateral and medial columns, the iliac bone was repaired. For example, with the cancellous bone inward and the cortical bone outward, the implanted bone and the condyle were fixed by various methods. All patients were given a memory compressive connector combined with Kirschner wire tension band or hollow screws for internal fixation. According to

the range of motion, the adhesive joint capsules and soft tissues around the elbow were loosened, and then the deep fascia and muscles behind it were sutured, so as to cover the internal fixators and bone blocks.

Outcome measures

(1) Surgical indicators: The patients were observed in terms of operative time (OT), length of hospital stays (LOSs), BUT (the patients had no local tenderness, longitudinal percussion pain, and local abnormal activities; X-ray examinations showed that the fracture line was fuzzy and some continuous calluses passed through the line), and wound healing time (WHT; excellent healing was Grade A, and primary healing with no adverse reactions was Grade B, and poor healing with inflammatory responses at the healing site was Grade C) and clinical healing time (CHT).

(2) The Visual Analogue Scale (VAS) [15] was used to evaluate the patients' pain severity before treatment, and one month and three months after treatment. The total score is 10 points, and higher VAS scores indicate severer pain.

(3) Detection of inflammatory cytokines: Before and after treatment, 5 mL of venous blood was extracted from the patients, centrifuged at 1500 × g (4°C, 10 minutes), and then stored in a refrigerator (-70°C) for later use. Enzyme-linked immunosorbent assay (ELISA) [16] was applied to detect the expression of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and nuclear factor kB (NF-kB), with reference to the instructions of human CRP kit (Gaochuang Chemical Technology Co., Ltd., Shanghai, China, pro-557), TNF-α kits (Biolab Science and Technology Co., Ltd., Beijing, China, ZN2460-QWJ), and NF-kB kits (Yaji Biological Engineering Co., Ltd., Shanghai, China, YS021-88B).

(4) The Mayo Elbow Performance Score (MEPS) [17] has a total score of 100 points and consists of four items, which included pain, motor function, stability, and daily activities. Higher MEPS scores indicate better functional recovery of elbow joint.

(5) Postoperative adverse reactions in both groups were observed and recorded.

(6) The patients' recovery was also measured and recorded. Their elbow movement was observed. Excellent indicates that the elbow joint is asymptomatic with 15° elbow extension and 130° elbow flexion; acceptable indicates that the elbow joint has slight symptoms with 30° elbow extension and 120° elbow flexion; fair indicates that the elbow joint has symptoms with 40° elbow extension and 90°-120° elbow flexion; poor indicates that the elbow extension is 40° and the elbow flexion is <90°. Excellence rate = excellent rate + acceptable rate.

(7) The Activity of Daily Living Scale (ADL) was used to evaluate the patients' postoperative QOL [18], with a full score of 100 points. A score of >60 points indicates mild life disorders; a score of 41-60 points indicates moderate life disorders; a score of 20-40 points indicates severe life disorders; a score of <20 points indicates complete disability. Higher ADL scores indicate better postoperative QOL.

Statistical methods

SPSS22.0 (Easy Bio System Inc., Beijing, China) was applied to statistical analysis. GraphPad Prism 7 was used for plotting figures. Count data were expressed as [n (%)], and compared between groups by a chi-square test. When the theoretical frequency in the test was less than 5, the comparison was conducted by a chi-square test with correction for continuity. Measurement data were expressed as mean ± standard deviation (mean ± SD), and compared between groups by an independent samples t test, with the comparison within groups before and after treatment conducted by a paired t test. $P<0.05$ indicated a statistically significant difference.

Results

Comparison of general information

The differences were not significant between the joint and control groups in gender, average age, body mass index (BMI), place of residence, nationality, educational backgrounds, history of smoking, history of drinking, causes of injury, and volume of bone defects ($P>0.05$). See **Table 1**.

Comparison of surgical indicators

OT was not significantly different between the joint and control groups ($P>0.05$), but LOSs,

Table 1. Comparison of general information [n (%)]/(mean ± SD)

Categories	Joint group (n = 101)	Control group (n = 83)	t/χ^2 value	*P* value
Gender			0.674	0.412
Male	56 (55.45)	51 (61.45)		
Female	45 (44.55)	32 (38.55)		
Average age (Years)	36.16 ± 2.45	35.57 ± 2.53	1.602	0.111
BMI (kg/m^2)	22.57 ± 3.48	23.03 ± 3.53	0.887	0.277
Place of residence			0.352	0.553
City	54 (53.47)	48 (57.83)		
Countryside	47 (46.53)	35 (42.17)		
Nationality			0.239	0.624
Han	56 (55.45)	49 (59.04)		
Ethnic minorities	45 (44.55)	34 (40.96)		
Educational backgrounds			0.427	0.513
≥ Senior high school	62 (61.39)	47 (56.63)		
< Senior high school	39 (38.61)	36 (43.37)		
History of smoking			0.128	0.720
Yes	55 (54.46)	43 (51.81)		
No	46 (45.54)	40 (48.19)		
History of drinking			2.740	0.098
Yes	68 (67.33)	46 (55.42)		
No	33 (32.67)	37 (44.58)		
Causes of injury			1.084	0.582
Traffic accident injury	34 (33.66)	34 (40.96)		
Weight crush	37 (36.63)	28 (33.73)		
Falling injury	30 (29.70)	21 (25.30)		
Volume of bone defects (cm^2)	2.38 ± 0.45	2.42 ± 0.42	0.618	0.537

BUT, WHT, and CHT were significantly better in the joint group (P<0.05). See **Table 2**.

Comparison of VAS scores at different time periods before and after treatment

Before treatment, the VAS scores were not significantly different between the joint and control groups (P>0.05). One and three months after treatment, the scores in both groups significantly reduced (P<0.05), and they were significantly lower in the joint group (P<0.05). See **Table 3**.

Comparison of expression of inflammatory cytokines before and after treatment

Before treatment, the expression of CRP, TNF-α, and NF-kB was not significantly different between the joint and control groups (P>0.05). After treatment, the improvement of the expression in both groups was significantly better than that before treatment (P<0.05), and it was significantly lower in the joint group (P<0.05). See **Figure 1**.

Comparison of MEPS scores at different time periods before and after treatment

Before treatment, the MEPS scores were not significantly different between the joint and control groups (P>0.05). One and three months after treatment, the scores in both groups significantly rose (P<0.05), and they were significantly higher in the joint group (P<0.05). See **Table 4**.

Comparison of complications after treatment

After treatment, the total incidence of complications was 3.96% in the joint group and 18.07% in the control group. The incidence was significantly lower in the joint group (P<0.05). See **Table 5**.

Comparison of recovery after treatment

After treatment, the excellence rate was 93.07% in the joint group and 77.11% in the control group. The post-treatment recovery of patients was significantly better in the joint group (P<0.05). See **Table 6**.

Comparison of ADL scores before and after treatment

Before treatment, the ADL scores were not significantly different between the joint and control groups (P>0.05). After treatment, the improvement of the scores in both groups was significantly better than that before treatment-significantly (P<0.05), and they were significantly higher in the joint group (P<0.05). See **Figure 2**.

Discussion

Clinically, the untimely diagnosis and treatment of bone defects, which are caused by

Table 2. Comparison of surgical indicators (mean ± SD)

Groups	n	OT (h)	LOSs (d)	BUT (Weeks)	WHT (Weeks)	BUT (Weeks)
Joint group	101	2.24 ± 0.45	17.56 ± 1.43	18.87 ± 2.34	2.83 ± 0.87	4.13 ± 0.64
Control group	83	2.16 ± 0.48	22.37 ± 1.94	22.68 ± 2.41	6.95 ± 1.09	6.03 ± 1.16
t	-	1.164	19.340	10.840	15.970	14.070
P	-	0.246	<0.001	<0.001	<0.001	<0.001

Table 3. Comparison of VAS scores at different time periods before and after treatment (mean ± SD)

Groups	n	VAS scores		
		Before treatment	One month after treatment	Three months after treatment
Joint group	101	7.23 ± 0.68	5.86 ± 0.57	3.57 ± 0.36
Control group	83	7.35 ± 0.72	6.79 ± 0.46	4.26 ± 0.48
t	-	1.160	12.000	11.130
P	-	0.248	<0.001	<0.001

bone infection and severe trauma, leads to joint dysfunction and bone nonunion, relatively high disability rates, and a great decrease in QOL. Moreover, the bone defects over 2 cm cannot heal by themselves and need to be repaired [19]. BG is the most commonly used method for the repair, and ABG has the characteristics of no rejection, satisfactory bone induction, and low economic costs [20, 21]. The revascularization of grafted bones is crucial for the healing of non-vascularized autoplastic bones at the site of the bone defects; vascular growth factors provided in bone graft areas can promote neovascularization and shorten BUT [22, 23].

As a platelet concentrate that is prepared by the centrifugation of autologous whole blood, PRP contains epidermal growth factors, vascular endothelial growth factors, and platelet-derived growth factors, and it can promote cell proliferation and angiogenesis [24]. In our study, we used BG combined with PRP to treat HCBD patients, and found that the fracture healing and the functional recovery of elbow joint were obvious in the joint group. In the research of Nakkeeran KP et al., the combination of PRP, calcium sulfate, and ABG can enhance the density of bone defects and improve the bone regeneration of patients with jaw defects [25]. In a study by Chu W et al., ABG combined with PRP can significantly promote the new bone formation and the functional recovery of the affected limbs in patients with nonunion [26]. In our study, after treatment, the LOSs, BUT, WHT and CHT were significantly better in the joint group. This is due to the fact that PRP contains a large number of growth factors, fibronectins, celluloses, and that these promote the differentiation and proliferation of bone cells and the revascularization of grafted bones, thereby enhancing the ability of bone healing. According to previous reports, PRP can improve the shoulder joint functions and reduce the post-treatment pain of patients with partial rotator cuff tendon tears. One month and three months after treatment, the VAS scores were significantly lower in the joint group, which suggests that PRP can effectively relieve the pain of the patients. As reported by He Z and other researchers, the expression of inflammatory cytokines such as CRP significantly rises in patients with spinal tuberculosis and undergoing BG [27]. In our study, after treatment, the expression of CRP, TNF-α, and NF-kB was significantly lower in the joint group. This is because PRP contains many kinds of antibacterial proteins such as platelet factor 4 and activity-modifying proteins, which can inhibit the growth of bacteria and fungi, and inhibit inflammatory cytokines in the serum of HCBD patients.

Patients with bone defects have affected functions of the elbow joint, and ABG prolongs their BUT and then leads to the slow recovery of the functions [28, 29]. One month and three months after treatment, the MEPS scores were significantly higher in the joint group, which is due to the faster postoperative bone healing, the faster postoperative recovery, and the better early functional exercises in this group. Therefore, the functional recovery of the elbow joint in the joint group was better than that in the control group. The total incidence of complications was significantly lower in the joint group, indicating that PRP can accelerate wound repair and reduce postoperative wound

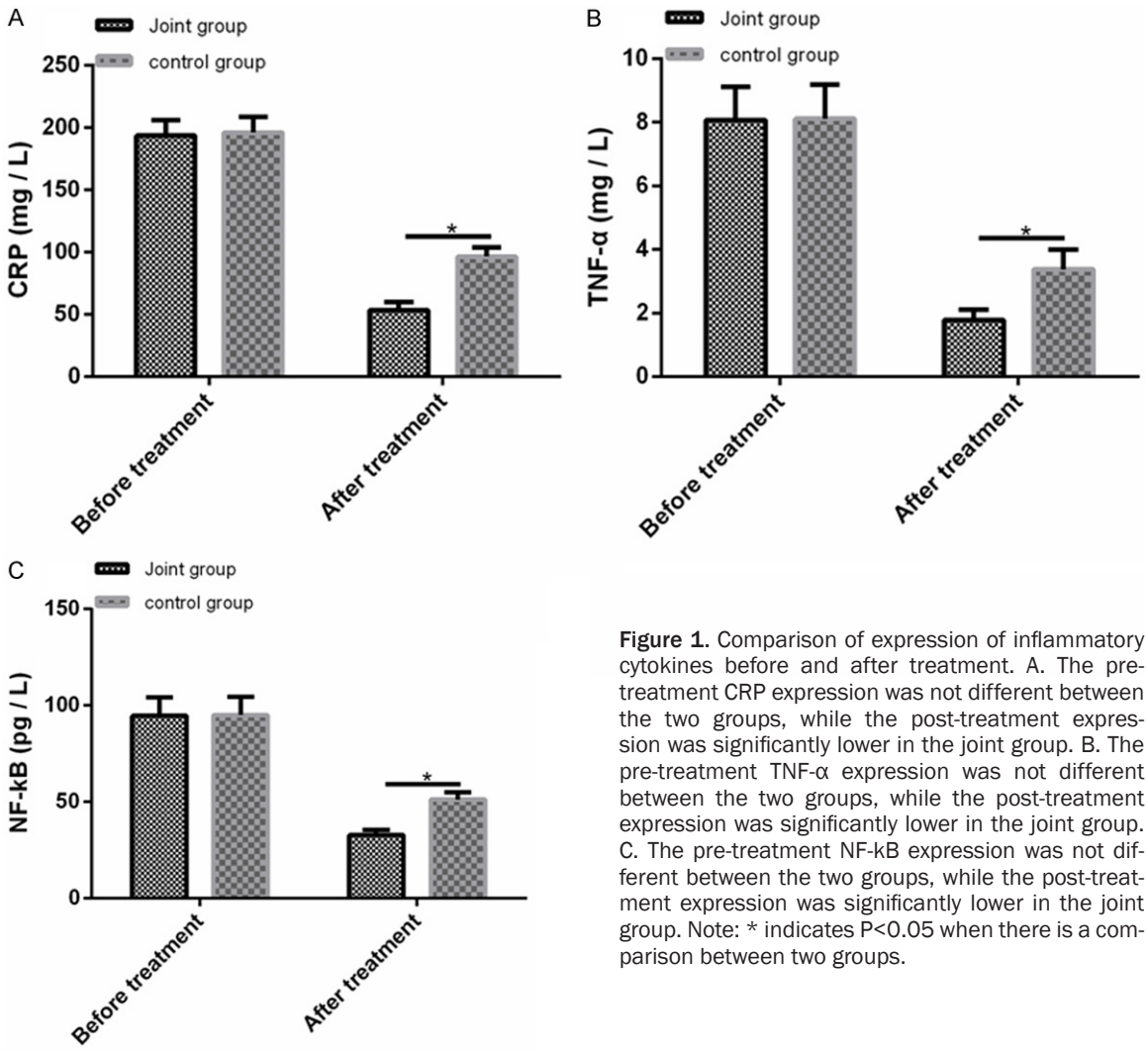

Figure 1. Comparison of expression of inflammatory cytokines before and after treatment. A. The pre-treatment CRP expression was not different between the two groups, while the post-treatment expression was significantly lower in the joint group. B. The pre-treatment TNF-α expression was not different between the two groups, while the post-treatment expression was significantly lower in the joint group. C. The pre-treatment NF-kB expression was not different between the two groups, while the post-treatment expression was significantly lower in the joint group. Note: * indicates P<0.05 when there is a comparison between two groups.

Table 4. Comparison of MEPS scores at different time periods before and after treatment (mean ± SD)

Groups	n	MEPS scores		
		Before treatment	One month after treatment	Three months after treatment
Joint group	101	45.68 ± 4.23	63.13 ± 5.23	79.68 ± 5.46
Control group	83	44.97 ± 4.27	54.31 ± 5.14	68.32 ± 5.34
t	-	1.128	11.470	14.180
P	-	0.261	<0.001	<0.001

bleeding. The post-treatment recovery in the joint group was significantly better than that in the control group, which suggests that the combined treatment of BG and PRP has satisfactory therapeutic effects on the HCBD patients. According to Schneppendahl J et al., for patients with large bone defects, autologous cancellous bone graft combined with PRP can improve the bone healing in cortical defect areas, and has remarkable efficacy [30]. This is similar to the results of this study. Bone defects affect patients' normal activities and reduce their QOL [31, 32]. In our study, after treatment, the ADL scores were significantly higher in the joint group. This reveals that for HCBD patients, the combined treatment can promote the healing of wounds and bones, relieve pain, and improve elbow functions, thus improving QOL.

In summary, for HCBD patients undergoing ABG, PRP can accelerate fracture healing, relieve pain, and improve the functions of the elbow joint. However, there are still limitations to this study. For instance, we have not obser-

Table 5. Comparison of complications after treatment [n (%)]

Items	Joint group (n = 101)	Control group (n = 83)	χ^2	P
Infection	2 (1.98)	6 (7.23)	3.018	0.082
Delayed healing	1 (0.99)	4 (4.82)	2.527	0.112
Bedsore	1 (0.99)	3 (3.61)	1.475	0.225
Deep vein thrombosis	0 (0.00)	2 (2.41)	2.460	0.117
Total incidence	4 (3.96)	15 (18.07)	9.789	0.002

Table 6. Comparison of recovery after treatment [n (%)]

Groups	n	Excellent	Acceptable	Fair	Poor	Excellence rate
Joint group	101	69 (68.32)	25 (24.75)	6 (5.94)	1 (0.99)	94 (93.07)
Control group	83	27 (32.53)	37 (44.58)	8 (9.64)	11 (13.25)	64 (77.11)
χ^2	-	-	-	-	-	9.565
P	-	-	-	-	-	0.002

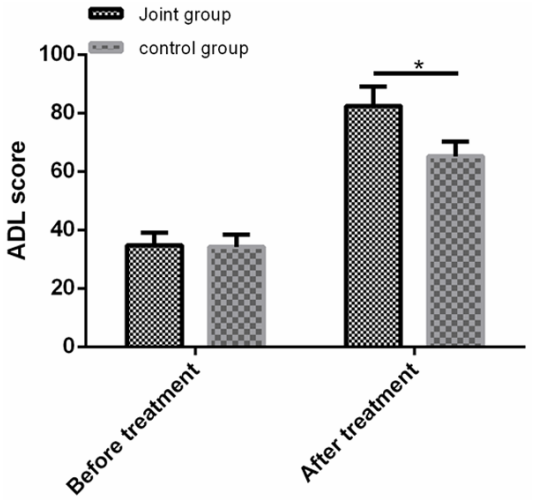

Figure 2. Comparison of ADL scores before and after treatment. The pre-treatment ADL scores were not different between the two groups, while the post-treatment scores were significantly higher in the joint group. Note: * indicates P<0.05 when there is a comparison between two groups.

ved whether PRP can produce a protective mechanism for the patients through other signaling pathways. In the future, we will gradually improve the research from the above perspective.

Disclosure of conflict of interest

None.

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