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Treatment of Optic Canal Decompression Combined with Umbilical Cord Mesenchymal Stem (Stromal) Cells for Indirect Traumatic Optic Neuropathy: A Phase 1 Clinical Trial

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Keywords
Mesenchymal stem cells · Retinal ganglion cells · Traumatic optic neuropathy · Clinical trial

Abstract
Purpose: This study was aimed to investigate the safety and feasibility of umbilical cord-derived mesenchymal stem cell (MSC) transplantation in patients with traumatic optic neuropathy (TON). ***Methods:*** This is a single-center, prospective, open-labeled phase 1 study that enrolled 20 patients with TON. Patients consecutively underwent either optic canal decompression combined with MSC local implantation treatment (group 1) or only optic canal decompression (group 2). Patients were evaluated on the first day, seventh day, first month, third month, and sixth month postoperatively. Adverse events, such as fever, urticarial lesions, nasal infection, and death, were recorded at each visit. The primary outcome was changes in best-corrected visual acuity. The secondary outcomes were changes in color vision, relative afferent pupillary defect, and flash visual evoked potential. ***Results:*** All 20 patients completed the 6-month follow-up. None of them had any systemic or ocular complications. The change in best-corrected visual acuity at follow-up was not significantly different between group 1 and group 2 ($p > 0.05$); however, group 1 showed better visual outcome than group 2. Both groups showed significant improvements in vision compared with the baseline ($p < 0.05$); however, there were no statistically significant differences between the groups ($p > 0.05$). In addition, no adverse events related to local transplantation were observed in the patients. ***Conclusions:*** A single, local MSC transplantation in the optic nerve is safe for patients with TON.

Introduction

Traumatic optic neuropathy (TON) is a direct or indirect injury that often results in serious damage to visual function, accounting for approximately 2% of closed craniocerebral injuries [1]. In direct injury, stress is directly applied to the optic nerve, with laceration due to an optical fracture. It often has poor prognosis. On the other hand, in indirect injuries, stress is transmitted to the soft tissues and skeleton, frequently leading to ischemia, inflammation, oxidative damage, and finally ganglion cell apoptosis [2, 3]. The current treatment for TON includes

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conservative management, high-dose steroids, optic canal decompression, and combined management. Although medical and surgical treatments have certain effect in some cases, there is still no proven treatment for TON [4]. Optic canal decompression can relieve local obstruction and compression; however, it still cannot change glial scar formation caused by the injured local microenvironment as well as the apoptosis of retinal ganglion cells (RGCs) [5]. Therefore, a new treatment strategy for TON is urgently warranted.

Owing to their neuroprotective, immunomodulatory, and regenerative properties, the therapeutic potential of mesenchymal stem cells (MSCs) has been widely studied in recent years in ophthalmic diseases, particularly in disorders that lead to a progressive and irreversible loss of vision [6]. A study has indicated that MSCs transplanted into the retina of cats can decrease RGC apoptosis and steadily express brain-derived neurotrophic factor [7]. The intravitreal transplants of dental pulp stem cells and bone marrow MSCs (BMSCs) promote significant neurotrophin-mediated RGC survival and axon regeneration after optic nerve injury [8, 9]. In addition, the intravitreal injection of human MSCs into the vitreous cavity of rats with acute optic nerve injury results in a decrease in RGC cell apoptosis and inflammation at the early stage [10]. BMSCs not only have the ability of tissue regeneration and repair but also have strong immune regulation and anti-inflammatory ability [11–13]. Furthermore, MSC transplantation significantly improves the prognosis of nerve injury by regulating the conversion of pro-inflammatory factors to anti-inflammatory factors at the injured site [14].

This study was aimed to investigate the safety and feasibility of MSC transplantation in patients with TON. To our knowledge, this is the first study in the literature that investigates the use of MSCs as a treatment option for patients with TON. Taken together, we conducted a phase 1 clinical trial of umbilical cord-derived human MSCs for the treatment of TON. This report summarizes the results of this trial.

Materials and Methods

Trial Design

This was a single-center, open-labeled phase 1 clinical trial to examine the safety and feasibility of MSCs in patients with TON (ChiCTR-TRC-14005093). The Ethics Committee affiliated to Daping Hospital, Military Medical University, approved this study (YIYANLUNSHEN No. (2014)004). The purpose of the study and its possible outcomes and adverse events were explained to all participants, and written informed consents were obtained. The study was conducted according to the tenets of the Declaration of Helsinki.

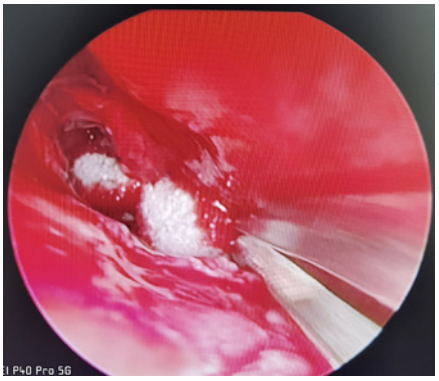

Fig. 1. Local MSC transplantation in group 1. The medial wall of the optic canal was removed under endoscopic optic canal decompression, and the optic nerve was covered using a MSC-gelatin sponge scaffold. Group 1: combined local MSC transplantation and optic canal decompression treatment. MSCs, mesenchymal stem cells.

Source and Preparation of MSCs

The isolation and culture of MSCs and their flow cytometry analyses were performed as previously described by our study group [15].

Preparation of MSC-Gelatin Sponge Scaffolds

Gelatin sponge scaffolds (porosity of approximately 80%, Nanjing, Jinling, China) were prepared by cutting sponges into sticks (length 18 mm, width 10 mm, and thickness 4 mm). MSCs at passage 2 were trypsinized, resuspended in MSC growth medium, and seeded onto the gelatin sponge scaffolds. In total, 1×10^6 cells in 600 μL of the culture medium were seeded into each scaffold and allowed to adhere to the bottoms of 12-well plates for 1 h. Then, the MSC-gelatin sponge scaffolds were additionally incubated in 1 mL of MSC growth medium for 24 h.

Patient Eligibility

People were enrolled in ophthalmology units at Daping Hospital, Military Medical University, between January 2015 and December 2017. The inclusion criteria were as follows: patients aged between 12 and 55 years, a clinical diagnosis of indirect TON, best-corrected visual acuity (BCVA) of <20/200, no previous treatment for TON, no previous congenital or acquired ophthalmological diseases hindering visual functions, and no systemic disease. The exclusion criteria were as follows: patients with penetrating trauma, other accompanying ocular lesions that cause decreased vision, media haziness, optic nerve avulsion, and direct TON.

Treatment Protocol

Patients were subsequently assigned to 2 treatment groups after obtaining informed consent; those who received endoscopic optic canal decompression and local MSCs transplantation were classified as group 1 and those who received only endoscopic optic canal de-

Table 1. Baseline characteristics of 2 groups

	Group-1	Group-2	Total (20)	*p* value
Age				
Mean (SD)	31.3 (17.5)	25 (12.31)	28.15 (15.08)	
Range	12–64	10–41	10–64	0.773
SE	5.33	3.89	3.37	
Male/female (%)	9/1 (90)	8/2 (80)	17/3 (85)	0.531
Trauma type, *n* (%)				
Car accident	1 (10)	2 (20)	3 (15)	
Hit	2 (20)	3 (30)	5 (25)	0.648
Falling	7 (70)	5 (50)	12 (60)	
Trauma to treatment time interval				
Mean (SD)	11 (10.26)	9 (10.51)	10 (10.16)	
Range	1–30	1–33	1–33	0.937
SE	3.25	3.32	2.27	
Pretreatment visual acuity				
Mean logMAR (SD)	2.82 (0.41)	2.84 (0.42)	2.83 (0.4)	
Range	1.7–3.1	1.7–3.1	1.7–3.1	0.936
SE	0.129	0.132	0.0898	
Color vision				
Mean (SD)	0.2 (0.63)	0.2 (0.63)	0.2 (0.616)	
Range	(0–2)	(0–2)	(0–2)	1
SE	0.2	0.2	0.138	
RAPD grading, *n* (%)				
1	1 (10)	1 (10)	2 (10)	
2	5 (0)	2 (20)	7 (35)	
3	2 (20)	4 (40)	6 (20)	
4	2 (20)	3 (30)	5 (25)	0.541
Mean (SD)	2.5 (0.97)	2.9 (0.99)	2.7 (0.98)	
Range	(1–4)	(1–4)	(1–4)	
SE	0.307	0.314	0.219	

RAPD, relative afferent pupillary defect.

compression were classified as group 2. All patients received endoscopic optic canal decompression under general anesthesia. Cotton swabs were soaked in 1:100,000 epinephrine solution and placed in the nasal cavity to ensure vasoconstriction. To expose the ostium of the sphenoid sinus, the superior turbinate was removed. The sphenoid sinus was opened and the posterior ethmoids were slightly opened. Then, the ostium was enlarged to the lateral wall to identify the optic nerve canal. The medial wall of the optic canal was thinned using a microdrill. The width is approximately one-half the cross-sectional diameter of the optic canal. The optic nerve sheath was incised at multiple points using a sharp 9# MVR scalpel. Finally, the operating field of the optic canal was covered using a MSC-gelatin sponge scaffold with a cell viability of 95% for group 1 and only with a sterile gelatin sponge scaffold for group 2 (Fig. 1). Patients were evaluated before treatment and at the first day, seventh day, first month, third month, and sixth month postoperatively.

Outcome Measures

Adverse events, such as fever, urticarial lesions, nasal infection, and death, were recorded at each visit and described in terms of incidence, severity, and relatedness with local MSC transplantation. The primary outcome was changes in BCVA. Visual acuity was measured using the international visual chart after best spectacle correction and transferred to logMAR value during statistical analysis. No light perception was assumed to be 3.1. The secondary outcomes were color vision, relative afferent pupillary defect (RAPD) grading, and flash visual evoked potential (FVEP). Color vision score was considered 0 in patients whose visual acuity was too low to observe any plate for comparing the pre- with post-treatment color vision mean scores.

Statistical Analysis

Data are presented as mean ± standard deviation and frequency (%). SPSS version 22.0 (IBM Corporation, Chicago, IL, USA) was used for statistical analyses. The *t* test was used for the comparison of normal numeric parameters. The χ^2 test was used for comparison of ranked data. Repeated measures ANOVA was used to analyze the time to event. The level of significance was considered as $p < 0.05$.

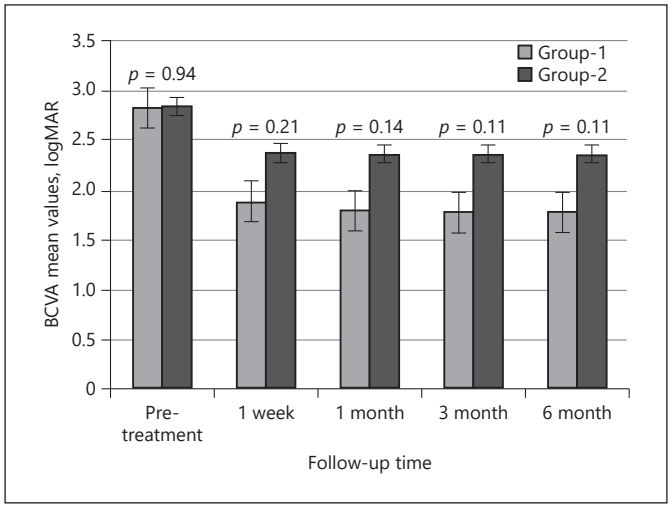

Fig. 2. BCVA at different time intervals in patients with TON in the 2 treatment groups. Group 1: combined local MSC transplantation and optic canal decompression treatment; group 2: optic canal decompression treatment. TON, traumatic optic neuropathy; BCVA, best-corrected visual acuity; MSC, mesenchymal stem cell.

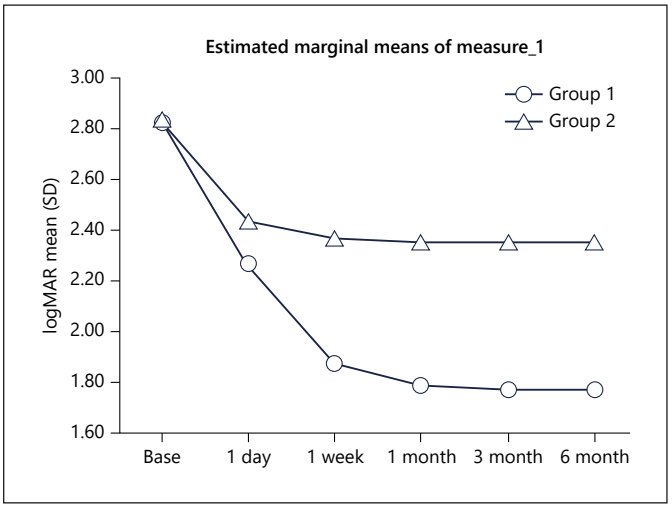

Fig. 3. Comparing the changes in mean visual logMAR in patients with TON during the follow-up period in the 2 treatment groups. Group 1: combined local MSC transplantation and optic canal decompression treatment; group 2: optic canal decompression treatment. TON, traumatic optic neuropathy; MSC, mesenchymal stem cell.

Results

We evaluated 20 patients with TON. The mean age of the included patients was 28.15 ± 15.07 (range, 10–64) years. Of the 20 patients, 2 (10%) were females. Demographics and pretreatment variables, such as age, trauma type, time interval from injury to treatment, and visual functions (BCVA, color vision, RAPD, and FVEP) were not significantly different between the 2 groups (Table 1).

There was no significant difference between the 2 groups at each time point ($p > 0.05$) (Fig. 2). Compared with the baseline, the 2 groups showed significant improvement in vision at 1 week postoperatively ($p < 0.05$) (Fig. 3). Group 1 showed a significant improvement in vision within 1 week and continued to improve at 1 month and reached a plateau 1 month after the treatment. Group 2 showed vision improvement up to 1 week and then started to reach a plateau (Fig. 3). Compared with the baseline, visual acuity was significantly improved in both groups 1 and 2 postoperatively ($p < 0.05$) (Table 2).

Compared with the baseline, color vision improvement was observed in group 1 at 3–6 months postoperatively ($p < 0.05$), whereas group 2 had no significant color vision improvement during follow-up ($p > 0.05$). There was no statistically significant difference between the 2 groups at the sixth month ($p > 0.05$) (Table 2).

Compared with the baseline, RAPD was significantly improved in group 1 at 1–6 months postoperatively ($p < 0.05$) and was significantly different in group 2 at each time point ($p < 0.05$) (Table 2). At the sixth month, there was no statistically significant difference between the 2 groups ($p > 0.05$).

FVEP could not be recorded in 3 patients (30%) in group 1 and in 4 patients (40%) in group 2 for bad visual acuity. The amplitude and latent periods of FVEP were not significantly different between the 2 groups during the 6-month follow-up ($p > 0.05$) (Table 3). However, compared with the baseline, the amplitude of P2 wave in group 1 was significantly higher in the sixth month ($p < 0.05$) (Table 3).

No serious adverse events were observed in the trial with respect to local implantation (Table 4). Cerebrospinal leak was observed in 1 patient in group 1, which was related to surgery.

Discussion/Conclusion

RGCs are specialized cells that transmit visual information to the brain and form the nervous visual system. Light is detected by the rods and cones of the retina, which then transform it into electrical signals and pass them to the bipolar cells and then to RGCs. Ganglion cell axons

Table 2. Changes of visual functions during follow-up

	Group-1					Group-2					*p* value[§]
	base	1 wk	1 mo	3 mo	6 mo	base	1 wk	1 mo	3 mo	6 mo	
Visual acuity											
Mean (SD)	2.82 (0.41)	1.88 (1.01)	1.79 (1.099)	1.77 (1.11)	1.77 (1.11)	2.84 (0.42)	2.37 (0.79)	2.36 (0.81)	2.36 (0.81)	2.36 (0.81)	0.113
Range	1.7–3.1	0.5–3.1	0.3–3.1	0.3–3.1	0.3–3.1	1.7–3.1	1.1–3.1	1–3.1	1–3.1	1–3.1	
SE	0.091	0.23	0.246	0.249	0.249	0.093	0.177	0.181	0.181	0.181	
p value		0.008	0.007	0.007	0.007		0.046	0.048	0.048	0.048	
Color vision											
Mean (SD)	0.2 (0.63)	0.7 (1.34)	2 (2.62)	2.7 (3.34)	2.7 (3.34)	0.2 (0.63)	0.7 (1.16)	1.5 (2.46)	1.5 (2.46)	1.5 (2.46)	0.433
Range	0–2	0–4	0–8	0–10	0–10	0–2	0–3	0–6	0–6)	(0–6	
SE	0.141	0.299	0.587	0.746	0.746	0.141	0.259	0.55	0.55	0.55	
p value		0.096	0.051	0.041	0.041		0.111	0.096	0.096	0.096	
RAPD grading, *n* (%)											
1	1 (10)	3 (30)	6 (60)	6 (60)	6 (60)	1 (10)	2 (20)	4 (40)	4 (40)	4 (40)	0.706
2	5 (50)	4 (40)	1 (10)	1 (10)	1 (10)	2 (20)	3 (30)	3 (30)	3 (30)	3 (30)	
3	2 (20)	1 (10)	1 (10)	1 (10)	1 (10)	4 (40)	3 (30)	1 (10)	1 (10)	1 (10)	
4	2 (20)	2 (20)	2 (20)	2 (20)	2 (20)	3 (30)	2 (20)	2 (20)	2 (20)	2 (20)	
Mean (SD)	2.5 (0.97)	2.2 (1.14)	1.9 (1.29)	1.9 (1.29)	1.9 (1.29)	2.9 (0.99)	2.5 (1.08)	2.1 (1.97)	2.1 (1.97)	2.1 (1.97)	
Range	(1–4)	(1–4)	(1–4)	(1–4)	(1–4)	(1–4)	(1–4)	(1–4)	(1–4)	(1–4)	
SE	0.22	0.25	0.29	0.29	0.29	0.22	0.24	0.27	0.27	0.27	
p value		0.081	0.005	0.005	0.005		0.037	0.011	0.011	0.011	

1 wk, first week; 1 mo, first month; 3 mo, third month; 6 mo, sixth month; RAPD, relative afferent pupillary defect. [§] *p* value for comparing sixth month of 2 groups; *p* value for comparing to base at each time point of each group, respectively.

Table 3. Changes of FEVP

	Group 1		Group 2		*p* value[§]
	pretreatment	6th month	pretreatment	6th month	
Amplitude, μV	6.50±4.08	7.83±4.69	5.75±1.91	7.78±4.30	0.986
p value		0.025		0.342	
Latent periods, ms	115.86±15.79	117.43±13.33	115.17±11.62	117.42±16.24	0.999
p value		0.476		0.409	

FVEP, flash visual evoked potential. [§] *p* value for comparing 6th month of 2 groups; *p* value for comparing to base of each group, respectively.

comprise the nerve fiber layer of the retina and converge to form the optic nerve; the signals then are propagated through the optic nerves to the optic chiasm and terminate from the lateral geniculate body to the occipital cortex, where they are translated into perceptions and light-mediated behaviors. RGCs are important in the visual system; if RGCs are dead or dysfunctional, even when the rest of the visual system is healthy, vision is impaired [16]. After primary head trauma, secondary injuries may cause further damage to the optic nerve, including ischemia, inflammation, oxidative damage, and glial proliferation, eventually leading to RGC apoptosis and glial scar formation. These events in turn result in serious vision loss in

Table 4. Safety profile

Adverse event	Group 1, %	Group 2, %
Transplant related AE		
Fever	0	0
Urticarial lesions	0	0
Nasal infection	0	0
AE during follow-up		
Fatal	0	0
Serious	0	0

Group 1: combined MSC local transplantation and optic canal decompression treatment; group 2, optic canal decompression treatment. AE, adverse event; MSCs, mesenchymal stem cells.

patients with TON. The probable approach to maintain vision involves the prevention of RGC apoptosis and glial scar formation.

MSCs are multipotent, self-renewing, and highly proliferative with differentiation abilities. They have neuroprotective effects and extraordinary immunomodulatory properties and are easy to isolate and expand rapidly. Owing to these features, MSCs were widely studied in neural and retinal diseases [17]. Zwart et al. [18] found that MSC transplantation into the lesion site prevented RGC apoptosis in a rat tract model. The neuroprotective effect of MSCs may be attributed to them secreting immunomodulatory and neurotrophic factors, such as TGF-β1, CNTF, NT-3, and brain-derived neurotrophic factor. Osborne et al. [19] found that hMSCs produce neurotrophins, which promote the survival and regeneration of injured RGCs in human retinal explants. In addition, another study found that the intravitreal transplantation of MSCs not only resulted in the secretion of neurotrophic factors but also the modulation of glial cell activation [20]. These successful results encourage the clinical applications of stem cells in patient with TON.

Our research is a phase 1 clinical trial to assess the safety and feasibility of allogeneic umbilical cord-derived human MSCs in patients with TON. We found that MSC transplantation was well-tolerated in this phase 1 trial in 10 patients with TON, without serious adverse events. Moreover, we followed up the patients for up to 6 months following MSC transplantation to confirm the short-term safety of MSCs for TON. To our knowledge, our research documented the first clinical trial of the use of umbilical cord-derived MSCs for TON.

In our research, the change in BCVA at follow-up was not significantly different between the 2 groups; however, group 1 showed better visual outcome than group 2. Both groups had significant improvements in visual acuity after treatment. Color vision improvement was observed in group 1 at 3–6 months postoperatively, and RAPD was significantly improved in both the groups. The amplitude of P2 wave was significantly higher at the sixth month in group 1 ($p < 0.05$ vs. baseline). Our results revealed that MSC transplantation did not show better visual acuity than optic canal decompression, which may be due to limited samples and poor visual acuity before treatment. The recovery of visual acuity in group 1 lasted for 1 month and then leveled off, whereas that in group 2 stabilized 1 week postoperatively. This may be due to the neuroprotective effect of MSCs. Zhao et al. [21] found that 7 days after MSC transplantation in a TON rat model, the number of RGCs was significantly increased and the number of RGCs was still more than that in the model group even at the 28th day. Chen et al. [10] found that transplanted hUCB-MSCs improved the survival of RGCs within 14 days, whereas RGCs died within 7 days in the control group. These results indicate that the neuroprotective effect of MSCs may last for nearly 14 days to 1 month and that MSCs proliferation after transplant affects the neuroprotective effect.

Many researchers have transplanted MSCs via intravitreal injection in both experimental and clinical trials to treat optic neuropathies or retinal diseases [22]. In our study, we transplanted MSCs into a gelatin sponge and placed the sponge on the optic nerve after optic nerve decompression. MSCs were transplanted onto the injury site to change the microenvironment and repair optic nerve damage as well as to avoid intraocular infection. Gelatin sponge has excellent cytocompatibility and histocompatibility. These characteristics are conducive to the growth and proliferation of MSCs [23]. The use of the gelatin sponge as an MSC scaffold in rat spinal cord transection revealed the neuroprotective effect of MSCs and demonstrated the better survival rate of the grafted MSCs as well as well as the promotion of axonal regeneration [24]. In our study, visual acuity improved within 1 month in group 1 and within 1 week in group 2. This suggests that transplanted MSC-gelatin sponge scaffolds have good survival capability. However, the neuroprotective effect of transplanted MSCs may depend on the cell viability and proliferation of MSCs at the injured site.

In conclusion, this phase 1 clinical trial used a single MSC transplantation that was well-tolerated and safe in patients with TON. There were no serious adverse events related to MSC transplantation in the 6-month follow-up period. However, this small sample size phase 1 trial has some limitations. First, with only 20 patients and the 6-month follow-up schedule, we can only draw a conclusion regarding the short-term safety but not about the efficacy of MSCs for TON. Second, the absence of any significant differences in clinical outcomes should be considered as a result of the small sample size and lack of statistical power rather than to the confirmation of the lack of a therapeutic effect. Third, the study design was inevitably changed because some patients did not provide consent for randomization. Finally, the limitations of a small sample size are further amplified by patients with poor visual function who were blinded while conducting the clinical trials. Thus, in a further research of this trial, we will enroll more patients using a stratified analysis method to try to generalize much more reliable conclusions.

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Statement of Ethics

The Ethics Committee affiliated to Daping Hospital, Military Medical University, approved this study (YIYANLUNSHEN No. (2014)004). Written informed consent was obtained either from the patient or their appointed legal guardian. The study was conducted according to the tenets of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Xiang Xu and Hongfeng Yuan contributed to study design, had full access to all the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis, including, especially, any adverse effect. Xu Bai and Xiaoyue Guan contributed to the data analysis and interpretation, and Jia Li contributed to writing of the manuscript.

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