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Original Article

Treatment efficacy of butylphthalide and sodium chloride injection combined with argatroban on neurological function and hemorheological parameters in ischemic stroke

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Abstract: Objective: To retrospectively analyze the effects of Butylphthalide and Sodium Chloride Injection (BP-SC) combined with Argatroban (AG) on neurological deficits and hemorheology in progressive ischemic stroke (PIS) patients. Methods: A total of 123 PIS patients admitted to our hospital between April 2023 and April 2025 were retrospectively analyzed and divided into two groups according to the different treatment schemes: the control group (n=58; treated with AG) and the research group (n=65; treated with BP-SC and AG). Clinical efficacy, neurological deficits (assessed by the National Institutes of Health Stroke Scale [NIHSS]), neurological function (astrocyte-derived protein S100β, brain-derived neurotrophic factor [BDNF], and neuron-specific enolase [NSE]), hemorheology (fibrinogen [FIB], plasma viscosity [PV], whole blood low-shear viscosity [WBLSV]), vascular endothelial function (endothelin-1 [ET-1] and nitric oxide [NO]), inflammatory factors (high-sensitivity C-reactive protein [hs-CRP], interleukin-6 [IL-6], and tumor necrosis factor-α [TNF-α]), adverse events (gingival bleeding, subcutaneous ecchymosis, nausea, abdominal distension, and vomiting), the 90-day post-operative modified Rankin Scale (mRS) score were compared between the two groups. Results: Compared with the control group, the research group demonstrated significantly higher overall effective rate and favorable prognosis rate. The research group also showed greater post-treatment reductions in the NIHSS score and levels of S100-β and NSE, along with a more pronounced elevation in BDNF level, indicating improved neuronal function. Additionally, the combined treatment significantly improved multiple hemorheological indices and endothelial function as evidenced by reduced ET-1 level and elevated NO level. Moreover, levels of hs-CRP, IL-6, and TNF-α were significantly decreased. However, the total incidence of adverse events was comparable between the two groups. Conclusion: Combined treatment with BP-SC and AG exerts more significant improvements in neurological deficits and hemorheological parameters in PIS patients.

Keywords: Butylphthalide and sodium chloride injection, argatroban, ischemic stroke, neurological deficits, hemorheology

Introduction

Stroke is the second leading cause of death and the third leading cause of disability worldwide, posing a great disease burden in Asia, despite a recent downward trend in its incidence [1, 2]. According to statistics, ischemic stroke (IS) accounts for approximately 43.5-76.1% of hospitalized acute stroke cases, with an age- and sex-standardized mortality rate of 43.3-222.6 cases per 100,000 person-years [2]. IS, also known as cerebral infarction, is a typical manifestation of stroke, occupying about 70% of all cases, mainly manifested as cerebral artery occlusion and cerebral tissue ischemia [3, 4]. Factors such as age, sex, diabetes, hyperlipidemia, and hyperhomocysteinemia are closely associated with IS [5]. The disease can lead to neurological deficits in patients, and the pathophysiological process is often accompanied by abnormal hemorheology [6]. Progressive IS (PIS) is characterized by persistent or stepwise aggravation of symptoms, poses substantial therapeutic challenges, and is associated with a poor prognosis [7]. Currently, no specific medicine is available for

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PIS, highlighting the need for further exploration.

Butylphthalide and Sodium Chloride Injection (BP-SC) is an anti-cerebral infarction preparation independently developed in China. Its main active component, dl-3-n-Butylphthalide, is a lipid-soluble compound capable of penetrating the blood-brain barrier (BBB) and is widely used for the treatment of acute IS (AIS) and its sequelae [8]. Cui et al. [9] reported that BP-SC effectively improved neurotransmitter levels and cerebral blood perfusion while also reducing oxidative stress in AIS cases. The arginine-derived Argatroban (AG) is a synthetic small-molecule direct thrombin inhibitor [10, 11]. It is widely used in the treatment of AIS, where it can effectively alleviate neurological deficits, improve activities of daily living, and help prevent thrombotic re-occlusion [12]. Given the limited research on the effects of BP-SC combined with AG on neurological deficits and hemorheology in IS patients, the present study was designed to address this gap and to provide additional evidence for optimizing treatment in this population.

The innovation of this study lies in the comprehensive evaluation of the clinical advantages of BP-SC combined with AG in the treatment of IS from the perspectives of clinical efficacy, neurological deficits, neurological function, hemorheology, vascular endothelial function, inflammatory markers, adverse events, and short-term prognosis. These findings provide reliable clinical evidence for the application of this therapy and offer a better treatment option for patients with ischemic stroke.

Information and methodology

Case selection

A total of 123 PIS patients admitted to the First Hospital of Hebei Medical University between April 2023 and April 2025 were retrospectively included in this study. Among them, 58 patients receiving AG therapy alone comprised the control group, while the other 65 cases treated with BP-SC combined with AG constituted the research group. This study was approved by the Ethics Committee of the First Hospital of Hebei Medical University.

Inclusion criteria: Patients who met the diagnostic criteria for PIS [13]; symptom onset within 48 hours, with the condition worsening in a stepwise or progressive manner; and complete clinical data available.

Exclusions criteria: Presence of cerebral hemorrhage, brain tumor, subarachnoid hemorrhage and hemorrhagic cerebral infarction; large-scale infarction with serious disturbance of consciousness; coagulation dysfunction; mental illness or severe dysfunction of major organs (heart, liver, kidneys); systemic hematologic diseases; contraindications to the study drugs; pregnancy or lactation.

Intervening methods

All patients received standard supportive therapies after admission, including measures to improve cerebral circulation and metabolism, as well as antiplatelet and lipid-lowering therapies.

Based on this, the control group was given AG (specification: 20 mL:10 mg, Shanghai Aladdin Biochemical Technology Co., Ltd., A408293). Within 48 hours of the symptom onset, 20 mL of AG was diluted in 28 mL of 0.9% sodium chloride solution (Shanghai Aladdin Biochemical Technology Co., Ltd., C111547) and administered via a constant-rate infusion pump (16 mL/h). After the first 48 h, the dosing was adjusted to every 12 hours for an additional 5 days. The total medication duration was 7 days.

On the basis of the above treatment, patients in the research group were additionally treated with BP-SC (specification: 100 mL:25 mg of butylphthalide and 0.9 g of sodium chloride; CSPC-NBP Pharmaceutical Co., Ltd., H20100041). BP-SC was administered by intravenous drip, starting within 48 hours of symptom onset, at a dose of 25 mg every 12 h, with each infusion lasting at least 50 minutes. The interval between two doses was more than 6 hours, and the treatment continued for 7 days.

During the treatment, liver and renal function parameters were closely monitored. Once any abnormalities were detected, the medication regimen was promptly adjusted.

Data collection

Treatment efficacy [14]: A reduction in the National Institutes of Health Stroke Scale (NIHSS) score of ≥90% was defined as cure; a reduction of 46%-89% was defined as marked effectiveness; a reduction of 18%-45% was defined as effectiveness; and a reduction of <18% was

defined as ineffectiveness. The total effectiveness rate was calculated as the percentage of patients classified as cured, marked effectiveness, and effectiveness.

Neurological deficits [15]: Neurological deficits were assessed using the NIHSS, with scores ranging from 0 to 42. The score is in direct proportion to neurological injury severity.

Neurological function: Venous blood (5 ml) was collected from each patient before treatment and 14 days after treatment. Serum was obtained after centrifugation, and the levels of astrocyte-derived protein S100-β, brain-derived neurotrophic factor (BDNF), and neuron-specific enolase (NSE) measurements were measured using enzyme-linked immunosorbent assay (ELISA). All procedures were carried out in strict accordance with the manufacturers' instructions for the corresponding ELISA kits (Shanghai Xuanke Biotechnology Co., Ltd., XK-E3573h, XK-E2991h, XK-E2245h).

Hemorheological parameters: Serum fibrinogen (FIB) levels were detected using automatic coagulation analyzer (Beijing MDmarker Biotechnology Co., Ltd., MD-1003) before and 14 days after treatment. Serum plasma viscosity (PV) and whole blood low-shear viscosity (WBLSV) were determined using an automatic blood rheology analyzer (Shanghai Scientific Instrument Co., Ltd., Y1318).

Vascular endothelial function: Serum endothelin-1 (ET-1; Shanghai Zaikang Biotechnology Co., Ltd., ZK-0028454) and nitric oxide (NO; Shanghai Lianmai Bio-engineering Co., Ltd., LM0023) levels were detected using radioimmunoassay and the nitrate reduction method, respectively.

Inflammatory markers: Serum levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were determined by ELISA before and 14 days post-treatment. All assays were conducted in strict accordance with the instructions of the corresponding ELISA reagent kits (Shanghai Xuanke Biotechnology Co., Ltd., XK-E1423h, XK-E1367h, XK-E2741h).

Adverse events: Adverse events, including gingival bleeding, subcutaneous ecchymosis, nausea, abdominal distension, and vomiting, were recorded during the treatment period, and the total incidence was calculated.

90-day favorable prognosis rate: Patient prognosis was assessed on day 90 after treatment using the modified Rankin Scale (mRS) [16]. A score ≤2 (0: asymptomatic; 1: no significant disability; 2: mild disability) was considered a favorable prognosis, whereas scores of 3-5 indicated moderate, severe, and extreme disability, respectively.

Among the above indicators, treatment efficacy, neurological deficits, and hemorheology were the primary endpoints, while neurological function, vascular endothelial function, inflammatory markers, adverse events, and 90-day favorable prognosis rate were the secondary outcomes.

Statistical analysis

SPSS 22.0 was used for statistical analyses. Measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$). Inter-group comparisons were conducted using independent-samples t-tests, while within-group comparisons at different time points were performed using paired t-tests. Count data were expressed as frequency and percentage [n (%)], and inter-group differences were assessed using the χ^2 test. A two-sided *P* value <0.05 was considered statistically significant.

Results

Comparison of baseline data between the two groups

As shown in **Table 1**, no significant differences were observed between the two cohorts in terms of sex, age, disease duration, or the prevalence of diabetes, hypertension, and dyslipidemia (all P>0.05), confirming good baseline comparability.

Comparison of therapeutic efficacy between the two groups

As shown in **Table 2**, the overall treatment effective rate in the research group was statistically higher compared to the control group (92.31% vs. 79.31%; P<0.05).

Comparison of NIHSS scores between the two groups

As shown in **Figure 1**, baseline NIHSS scores were comparable between the groups (P>0.05). After treatment, both groups demonstrated a

Table 1. Comparison of baseline characteristics between the two groups

Data	Control group (n=58)	Research group (n=65)	χ^2/t	P
Sex			0.018	0.892
Male	35 (60.34)	40 (61.54)		
Female	23 (39.66)	25 (38.46)		
Age (years)	55.29±6.91	56.42±6.90	0.906	0.367
Disease duration (h)	20.02±6.12	19.78±6.78	0.205	0.838
Diabetes	19 (32.76)	17 (26.15)	0.646	0.422
Hypertension	20 (34.48)	25 (38.46)	0.209	0.647
Dyslipidemia	16 (27.59)	20 (30.77)	0.150	0.699

Table 2. Comparison of clinical efficacy between the two groups

Therapeutic effectiveness	Control group (n=58)	Research group (n=65)	χ^2	P
Cure	17 (29.31)	28 (43.08)		
Marked effectiveness	16 (27.59)	20 (30.77)		
Effectiveness	13 (22.41)	12 (18.46)		
Ineffectiveness	12 (20.69)	5 (7.69)		
Overall effective rate	46 (79.31)	60 (92.31)	4.347	0.037

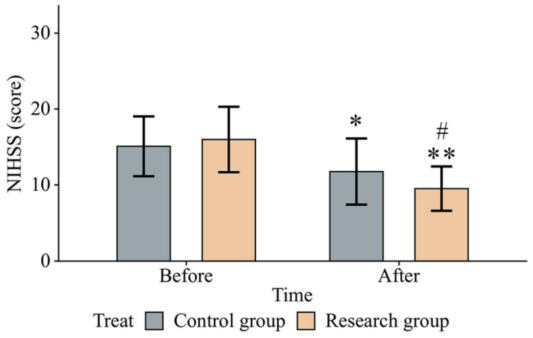

Figure 1. Comparison of NIHSS scores between the two groups before and after the treatment. NIHSS: National Institutes of Health Stroke Scale. *P<0.05, **P<0.01 vs. baseline level in the same group; #P<0.05 vs. the control group.

marked decline in NIHSS score (both P<0.05), with a more pronounced decrease observed in the research group relative to the control group (P<0.05).

Comparison of neurological function between the two groups

No significant differences were observed in the baseline serum levels of neurological biomarkers (S100-β, BDNF, and NSE) between the two groups (all P>0.05). Following the intervention, serum S100-β and NSE levels were significantly decreased, while BDNF levels were significantly increased in both groups (all P<0.05), with the research group exhibiting more pronounced decline/increase magnitude compared with the control group (all P<0.05) (**Table 3**).

Comparison of hemorheology between the two groups

As shown in **Figure 2**, baseline hemorheological parameters were comparable between the two groups (P>0.05). Following treatment, FIB, PV, and WBLSV significantly decreased in both cohorts (all P<0.05), and the reductions were more notable in the research group than in the control group (all P<0.05).

Comparison of vascular endothelial function between the two groups

Table 4 shows the baseline vascular endothelial function indices, including ET-1 and NO, showed no significant difference between the two groups (both P>0.05). After treatment, ET-1 levels were significantly decreased, whereas NO levels were significantly increased in both groups (all P<0.05). Notably, the research group showed significantly lower ET-1 and higher NO levels compared to the control group (P<0.05).

Comparison of inflammatory markers between the two groups

As shown in **Table 5**, baseline levels of inflammatory markers, including hs-CRP, IL-6, and TNF-α, were comparable between groups (P>

Table 3. Comparison of neurological function between the two groups

Indicators	Control group (n=58)	Research group (n=65)	t	P
S100-β (μg/L)				
Before	0.82±0.20	0.90±0.29	1.760	0.081
After	0.40±0.17*	0.30±0.13**	3.687	<0.001
BDNF (ng/mL)				
Before	3.59±0.88	3.31±0.77	1.882	0.062
After	4.38±0.94*	5.23±1.23**	4.267	<0.001
NSE (μg/L)				
Before	51.05±10.34	51.32±7.02	0.171	0.865
After	36.45±6.82*	24.20±8.86**	8.515	<0.001

Note: BDNF, brain-derived neurotrophic factor; NSE, neuron-specific enolase; *P<0.05, **P<0.01, vs. baseline levels.

0.05). After treatment, both groups exhibited marked reductions in all inflammatory factors (all P<0.05), with lower levels in the research group compared to controls (P<0.05).

Comparison of adverse events between the two groups

Recorded adverse events mainly included gingival bleeding, subcutaneous ecchymosis, nausea, abdominal distension, and vomiting. As summarized in **Table 6**, no significant difference was observed in the overall incidence of adverse events (21.54% vs. 17.24%; P>0.05) between the two groups.

Comparison of 90-day favorable prognosis rate between the two groups

According to the mRS assessment on post-treatment day 90 (**Table 7**), the proportion of patients with a favorable prognosis (mRS ≤2) in the research group was notably higher than the control group (83.08% vs. 65.52%; P<0.05).

Discussion

Patients with IS frequently present with neurological deficits, such as paralysis and aphasia, which are related to impaired cerebral blood circulation and ischemia and hypoxia related local tissue injury [17]. IS not only affects patients' quality of life by limiting normal occupational and social functioning, but also poses a heavy burden to patients and their families. Progressive IS (PIS) remains a major challenge and requires in-depth exploration of more effective therapies.

In this study, BP-SC combined with AG significantly improved treatment efficacy in PIS patients from 79.31% (AG monotherapy) to 92.31%. This may be attributed to butylphthalide, an active substance of BP-SC, which exerts multiple pharmacological effects, such as reducing inflammatory reaction, enhancing microcirculation, protecting mitochondria, reducing blood-brain barrier permeability, and improving nerve cell function [18]. These effects collectively contribute to the alleviation of neurological deficit-associated symptoms in PIS patients. Butylphthalide has demonstrated efficacy in inhibiting platelet aggregation and thrombosis formation. It significantly ameliorates hypercoagulable states and increases the number of circulating endothelial progenitor cells, thereby strengthening the vascular repair ability [9]. As a thrombin antagonist, AG plays a neuroprotective role by inhibiting inflammatory factor generation and reducing brain edema, thus improving neurological function [19]. An animal experiment demonstrated the significant neuroprotective effects of AG, as evidenced by marked improvements in learning and memory after focal ischemia compared with normal saline or thrombin [20]. Hence, combined therapy may exert synergistic, multi-target therapeutic effects in PIS patients, with AG providing anticoagulant protection and BP-SC contributing to the inhibition of platelet aggregation and enhancement of vascular repair.

Additionally, the combined treatment significantly alleviated neurological deficits in PIS patients, strengthened their self-care ability, and improved their neurological-related indexes. S100-β and NSE are well-established neuronal injury markers, with their down-regulation reflecting the repair of brain tissue injury [21].

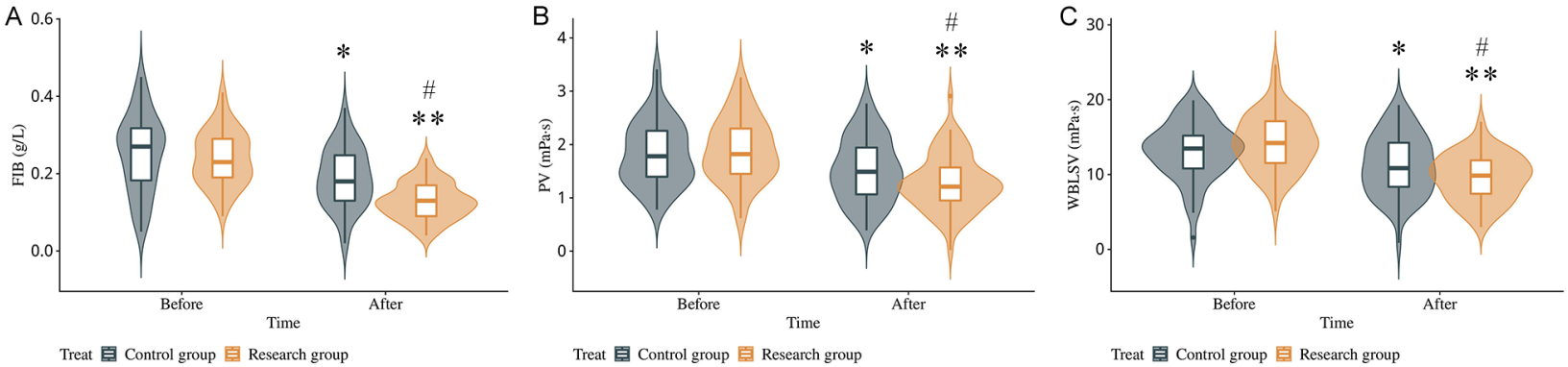

Figure 2. Comparison of hemorheological parameters between the two groups before and after the treatment. A. Fibrinogen (FIB); B. Plasma viscosity (PV); C. Whole blood low-shear viscosity (WBLSV). Note: *P<0.05, **P<0.01, *vs.* baseline level in the same group; $^{\#}$P<0.05 *vs.* the control group.

Table 4. Comparison of vascular endothelial function between the two groups

Indicators	Control group (n=58)	Research group (n=65)	t	P
ET-1 (ng/L)				
Before	70.95±9.16	71.05±10.88	0.055	0.956
After	63.91±8.82*	60.40±7.80**	2.342	0.021
NO (μmol/L)				
Before	32.38±4.44	32.85±5.52	0.516	0.607
After	43.50±5.41*	54.78±7.42**	9.534	<0.001

Note: ET-1, endothelin-1; NO, nitric oxide. *P<0.05, **P<0.01, vs. baseline levels.

Table 5. Comparison of inflammatory factors between the two groups

Indicators	Control group (n=58)	Research group (n=65)	t	P
hs-CRP (mg/L)				
Before	12.80±4.06	11.88±3.85	1.289	0.200
After	8.07±2.87*	5.98±2.67**	4.183	<0.001
IL-6 (ng/L)				
Before	25.17±3.90	24.29±5.35	1.032	0.304
After	17.91±4.52*	13.98±3.68**	5.310	<0.001
TNF-α (ng/L)				
Before	34.50±5.21	35.52±6.02	0.999	0.320
After	29.38±5.68*	25.32±6.58**	3.642	<0.001

Note: hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α. *P<0.05, **P<0.01, vs. baseline levels.

Table 6. Comparison of the incidence of adverse events between the two groups

Indicators	Control group (n=58)	Research group (n=65)	χ^2	P
Gingival bleeding	3 (5.17)	4 (6.15)		
Subcutaneous ecchymosis	3 (5.17)	5 (7.69)		
Nausea	2 (3.45)	2 (3.08)		
Abdominal distension	1 (1.72)	2 (3.08)		
Vomiting	1 (1.72)	1 (1.54)		
Total	10 (17.24)	14 (21.54)	0.360	0.548

Table 7. Comparison of 90-day postoperative prognosis between the two groups

mRS score (points)	Control group (n=58)	Research group (n=65)	χ^2	P
0	9 (15.52)	14 (21.54)		
1	16 (27.59)	20 (30.77)		
2	13 (22.41)	20 (30.77)		
3	10 (17.24)	6 (9.23)		
4	6 (10.34)	4 (6.15)		
5	4 (6.90)	1 (1.54)		
Favorable prognosis (0-2)	38 (65.52)	54 (83.08)	5.013	0.025

Note: NRS: mRS, modified Rankin Scale.

BDNF, as one of the most widely distributed neurotrophic factors in mammalian brain, reflects the function and structural plasticity of the central nervous system (CNS) and plays an important role in neuroprotection [22]. In the report of Li et al. [23], BP-SC combined with

edaravone dexborneol improved clinical efficacy, relieved neurological deficits, enhanced self-care, and inhibited serum inflammatory factors in PIS patients, similar to the results of this study.

Furthermore, BP-SC combined with AG significantly improved hemorheological parameters and vascular endothelial function in PIS patients compared with AG monotherapy, as evidenced by favorable changes in ET-1 and NO levels, which are essential for maintaining vascular tone and normal blood flow. AIS impairs vascular endothelial function, resulting in a notable increase in ET-1 levels and reduction in NO levels. Eventually, this causes abnormal vascular contraction and relaxation, thereby aggravating cerebral ischemia, hypoxia, and cerebral edema [24]. In the study of Wang et al. [25], BP-SC combined with atorvastatin calcium tablets improved neurological function and cerebral hemodynamics in patients with AIS, similar to the results of this study. Meanwhile, BP-SC combined with AG significantly inhibited serum levels of hs-CRP, IL-6, and TNF-α, demonstrating pronounced anti-inflammatory effects.

In terms of safety, the combined therapy did not significantly increase the risk of total adverse events such as gingival bleeding, subcutaneous ecchymosis, nausea, abdominal distension, and vomiting, suggesting its tolerability. In the report of Zhang et al. [26], the sequential treatment of butylphthalide is helpful to improve neurological/cognitive functions and collateral circulation in patients with AIS on the premise of not compromising safety, which aligns with our findings. Finally, the 90-day favorable prognosis rate was markedly higher in PIS patients receiving combined treatment than those receiving AG monotherapy (83.08% vs. 65.52%). Consistently, previous studies have reported that butylphthalide combined with human urinary kallidinogenase improves the independence rate of patients with AIS 6 months after onset, without causing serious adverse events [27].

Inevitably, this study has several limitations. First, the potential mechanisms underlying the combined treatment of BP-SC and AG for PIS was not investigated. Second, the follow-up period was relatively short, and an extended follow-up of 5-10 years would further clarify the long-term clinical advantages of the combined therapy. Finally, treatment cost and economic benefits were not evaluated.

Conclusion

Compared to AG monotherapy, combination therapy with BP-SC enhances treatment efficacy, facilitates neurological recovery, and improves hemorheological parameters, endothelial function, and 90-day favorable prognosis in PIS patients. In addition, it effectively reduces serum inflammatory markers while demonstrating a comparable safety profile, supporting its broader clinical application.

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Disclosure of conflict of interest

None.

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