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Original Article

Efficacy, safety, and vascular endothelial function improvement of enalapril maleate-folic acid tablets in H-Type hypertension

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Abstract: Objective: To explore the clinical application value of Enalapril Maleate (EM)-Folic Acid (FA) Tablets in the treatment of H-type hypertension (HTHT), with a focus on evaluating its therapeutic efficacy, safety, and regulatory effects on vascular endothelial function. Methods: A retrospective analysis was conducted on 127 HTHT patients treated between March 2022 and January 2025. Patients were allocated into two groups: a control group (n=60) receiving EM monotherapy and a research group (n=67) receiving the EM-FA therapy. This study analyzed: ① overall therapeutic outcomes; ② blood pressure control; ③ stroke incidence; ④ drug-related adverse events; ⑤ lipid metabolism; ⑥ homocysteine (Hcy) levels; ⑦ vascular endothelial function; ⑧ serum inflammatory markers; and ⑨ hemorheological parameters. Results: Compared with the control group, the research group exhibited superior post-treatment outcomes. Specifically, overall treatment efficacy was improved; blood pressure control was more effective; lipid profiles improved significantly; Hcy levels decreased more significantly; vascular endothelial function was better restored; inflammatory factor levels decreased more substantially; hemorheological parameters were optimized; and the incidences of stroke and drug-related adverse events were notably reduced. Conclusions: EM-FA Tablets provide significant therapeutic benefits in managing HTHT, with enhanced safety and notable improvements in vascular endothelial function, underscoring their potential for widespread clinical application.

Keywords: Enalapril maleate-folic acid tablets, H-type hypertension, therapeutic outcomes, safety, vascular endothelial function

Introduction

Hypertension (HT), a highly prevalent cardiovascular disorder, increases in incidence with age and affects around 250 million individuals in China, accounting for nearly roughly 80% of cardiovascular disease [1]. A notable subset is H-type HT (HTHT), characterized by concurrent essential HT and elevated plasma homocysteine (Hcy ≥10 μmol/L), comprising about 80.3% of all HT cases [2]. Hcy, an intermediate metabolite in the methionine cycle, can accumulate excessively and cause hyperhomocysteinemia (HHcy). This condition impairs microvascular endothelial function in vital organs like the brain and kidneys, thereby elevating the risk of severe cardiocerebrovascular events, including chronic total coronary occlusion, atherosclerosis, and cerebral infarction [3, 4]. Research further suggests that lifestyle factors such as smoking, alcohol abuse, unhealthy eating patterns, and obesity may accelerate the onset and progression of HTHT [5]. The pathogenesis of HTHT is multifactorial. Genetic variations, particularly the methylenetetrahydrofolate reductase (MTHFR) gene polymorphism C667T (rs1801133), plays an important role [6]. However, therapeutic management of HTHT remains challenging, with current medications showing suboptimal outcomes, underscoring the urgent need for more effective treatment approaches [7].

Enalapril Maleate (EM) is widely prescribed for managing HT, though its efficacy as monotherapy remains limited [8]. After administration, EM

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is converted into its active metabolite, enalaprilat, which selectively inhibits angiotensin-converting enzyme (ACE), thus suppressing angiotensin II formation and promoting vasodilation [9]. Beyond blood pressure control, EM alleviates symptoms of heart failure, delays chronic kidney disease progression, reduces cardiac workload, decreases circulating blood volume, and inhibits pathological cardiovascular remodeling [10, 11]. EM-Folic Acid (FA) tablets represent a dual-component formulation, combining the antihypertensive effects of EM with the vascular-protective benefits of FA. FA, a vital vitamin with notable antioxidant capabilities, has been linked to a reduced incidence of cardiocerebrovascular events [12]. Adequate FA intake is especially critical during pregnancy, as prenatal FA supplementation can mitigate MTHFR C677T genotype polymorphism-associated risks, reducing the likelihood of HTHT in offspring [13]. Mechanistically, FA may exert antihypertensive effects by modulating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway, mitigating oxidative stress, and ameliorating HHcy-associated complications such as myocardial fibrosis and diastolic dysfunction [14].

This study explores the clinical application value of EM-FA tablets in patients with HTHT, focusing on therapeutic efficacy, medication safety, and improvements in vascular endothelial function, with the aim of providing an optimized treatment plan for this specific population.

Research subjects and methods

Case selection

This retrospective study included 127 patients diagnosed with HTHT who were treated at Xichang People's Hospital between March 2022 and January 2025. Therapy-based allocations were performed, with 60 cases receiving EM tablets assigned to the control group and 67 treated with EM-FA Tablets assigned to the research group. Baseline characteristics showed no significant inter-group differences ($P>0.05$), ensuring group comparability. The study protocol was approval by the Ethics Committee of Xichang People's Hospital. Power analysis for comparing dichotomous outcomes between two independent groups guided our sample size planning (two-sided $\alpha=0.05$, $1-\beta=80\%$). The required minimum sample size was 50 per group; actual enrollment exceeded this threshold (60 in the control group, 67 in the study group).

Inclusion and exclusion criteria

Inclusion Criteria: A diagnosis of HTHT according to the World Health Organization (WHO), characterized by plasma Hcy concentrations (Hcy) ≥10 μmol/L and systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg [15]; newly identified and treatment-naive patients; no limitations on study medications. Additionally, complete and detailed medical records.

Exclusion Criteria: prior use of FA or related compounds within the preceding three months; hepatic or renal dysfunction; thyroid hormone disorders; pregnancy or lactation; coagulation abnormalities; patients with pulmonary disease, peripheral vascular diseases, diabetes, malignancies, a seizure history, or psychiatric disorders.

Treatment methods

Both patient cohorts received oral antihypertensive care, including strict dietary sodium and fat restriction, medication adherence supervision, smoking/alcohol cessation support, disease-specific health education, as well as cardiac rehabilitation training. The therapeutic course spanned one month.

Control group: Patients were treated with EM monotherapy, administered at a dose of 10 mg once daily (5 mg/tablet × 2 tablets).

Research group: Patients received EM-FA tablets (each tablet containing 10 mg enalapril and 0.8 mg FA), administered as one tablet once daily.

Clinical observation indicators

(1) Therapeutic efficacy. ① Markedly Effective: Post-treatment serum Hcy levels and arterial blood pressure returned to the normal reference range. ② Effective: Post-treatment Hcy levels decreased by approximately 16%, with SBP/DBP reductions exceeding 10 mmHg but not reaching the normal standard. ③ Ineffective: Minimal or no change in Hcy or blood pressure after treatment. Total Effective Rate = Markedly Effective Rate + Effective Rate.

Table 1. Comparison of baseline characteristics between the two groups

Indicators	Control group (n=60)	Research group (n=67)	t/χ^2	P
Sex			1.972	0.160
Male	37 (61.67)	33 (49.25)		
Female	23 (38.33)	34 (50.75)		
Age (years)	60.75±9.70	61.97±12.59	0.606	0.545
Body mass index (kg/m^2)	24.88±3.02	24.98±3.58	0.169	0.866
Duration of hypertension (year)	3.50±5.48	3.85±5.83	0.347	0.729
Comorbid diabetes	8 (13.33)	10 (14.93)	0.066	0.797
Comorbid coronary heart disease	3 (5.00)	7 (10.45)	1.295	0.255

(2) Blood pressure monitoring. SBP and DBP were measured in a seated position at rest using a calibrated electronic sphygmomanometer. Each measurement lasted about 60 seconds. Three measurements were taken at 1-2 min intervals, with the mean value recorded as the final value.

(3) Incidence of stroke. Post-treatment cerebrovascular events, including subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction, were tracked to determine event rates.

(4) Drug-related adverse events (DRAE). During treatment, DRAEs - including gastrointestinal symptoms (e.g., nausea), respiratory manifestations (e.g., cough), and neurological effects (e.g., vertigo) - were documented. The cumulative incidence of DRAEs was quantified.

(5) Blood lipid profile. Fasting venous blood samples (5 mL) were collected before and after treatment. Following centrifugation, serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were determined utilizing an automated biochemistry analyzer.

(6) Hcy and vascular endothelial function. Serum Hcy was measured using an enzymatic cycling assay. Nitric oxide (NO) was examined employing the nitrate reductase technique, whereas radioimmunoassay was utilized to determine endothelin-1 (ET-1) concentrations.

(7) Inflammatory markers. Enzyme-linked immunosorbent assay (ELISA) was employed to measure serum concentrations of interleukin (IL)-6/8 and high-sensitivity C-reactive protein (hs-CRP).

(8) Hemorheological parameters. Hematocrit (HCT) was evaluated using an automated hematology analyzer. Capillary viscometry was applied to assess plasma viscosity (PV), and the platelet aggregation rate (PAR) was determined via platelet aggregation testing (PAgT).

Statistical methods

For continuous variables, data were described using mean ± standard error of the mean (mean ± SEM) for descriptive statistics. Independent samples t-tests were utilized to examine intergroup differences, while paired t-tests were employed for within-group comparisons before and after intervention. For categorical variables, proportions (percentages) were used for statistical description, and intergroup comparisons were performed using chi-square tests (χ^2 tests). All experimental data were processed using SPSS 20.0 statistical software, adopting $P<0.05$ as the threshold for statistical significance.

Results

Baseline characteristics

Baseline demographic and clinical characteristics of the two groups are summarized in **Table 1**. No significant differences were observed in gender distribution, mean age, body mass index (BMI), duration of hypertension, or comorbidities (diabetes and coronary heart disease) (all $P>0.05$), indicating comparability between the groups.

Therapeutic outcomes

As outlined in **Table 2**, the research group exhibited a markedly higher overall effective rate compared to the control group ($P<0.05$).

Table 2. Comparison of therapeutic outcomes between the two groups

Indicators	Control group (n=60)	Research group (n=67)	χ^2	P
Markedly effective	26 (43.33)	35 (52.24)		
Effective	20 (33.33)	27 (40.30)		
Ineffective	14 (23.33)	5 (7.46)		
Overall effective rate	46 (76.67)	62 (92.54)	6.267	0.012

Table 3. Comparison of blood pressure between the two groups before and after treatment

Indicators	Control group (n=60)	Research group (n=67)	t	P
SBP (mmHg)				
Before intervention	149.70±10.77	150.93±11.49	0.620	0.536
After intervention	139.25±13.00*	130.99±9.91**	4.051	<0.001
DBP (mmHg)				
Before intervention	102.72±11.81	99.72±10.84	1.493	0.138
After intervention	86.42±9.70*	82.48±6.97**	2.648	0.009

Notes: SBP, systolic blood pressure; DBP, diastolic blood pressure. *P<0.05 and **P<0.01, compare with baseline value.

Table 4. Comparison of incidence of stroke events between the two groups

Indicators	Control group (n=60)	Research group (n=67)	χ^2	P
Subarachnoid hemorrhage	1 (1.67)	0 (0.00)		
Intracerebral hemorrhage	4 (6.67)	1 (1.49)		
Cerebral Infarction	2 (3.33)	0 (0.00)		
Total	7 (11.67)	1 (1.49)	5.551	0.019

Table 5. Comparison of incidence of drug-related adverse events between the two groups

Indicators	Control group (n=60)	Research group (n=67)	χ^2	P
Nausea	5 (8.33)	3 (4.48)		
Cough	4 (6.67)	3 (4.48)		
Vertigo	6 (10.00)	0 (0.00)		
Total	15 (25.00)	6 (8.96)	5.904	0.015

Blood pressure indicators

Table 3 presents the SBP and DBP levels in both groups before and after treatment. Baseline SBP and DBP measurements did not differ significantly between the two cohorts (P> 0.05). Post-intervention, both groups experienced substantial declines in blood pressure; however, the research group demonstrated a significantly greater reduction in both SBP and DBP (P<0.05).

Stroke events

As shown in **Table 4**, the incidence of averse events, including subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke, was markedly lower in the research group (1.49%, with only one case of intracerebral hemorrhage), compared with the control group (11.67%) (P<0.05).

Comparison of DRAEs

An inter-group comparison was made regarding DRAEs such as nausea, cough, and vertigo during treatment (**Table 5**). The research group exhibited a substantially lower overall incidence of DRAEs (8.96%) relative to the control group (25.00%) (P<0.05).

Blood lipid profiles

As depicted in **Figure 1**, there were no significant intergroup differences in TC, TG, LDL-C, or HDL-C levels at baseline (P>0.05). Following the intervention, both groups experienced notable reductions in TC, TG, and LDL-C, alongside an elevation in HDL-C (P<0.05). Notably, the research group achieved more pronounced lipid profile improvements, with significantly lower TC, TG, and LDL-C levels and higher HDL-C levels compared to the control group (P<0.05).

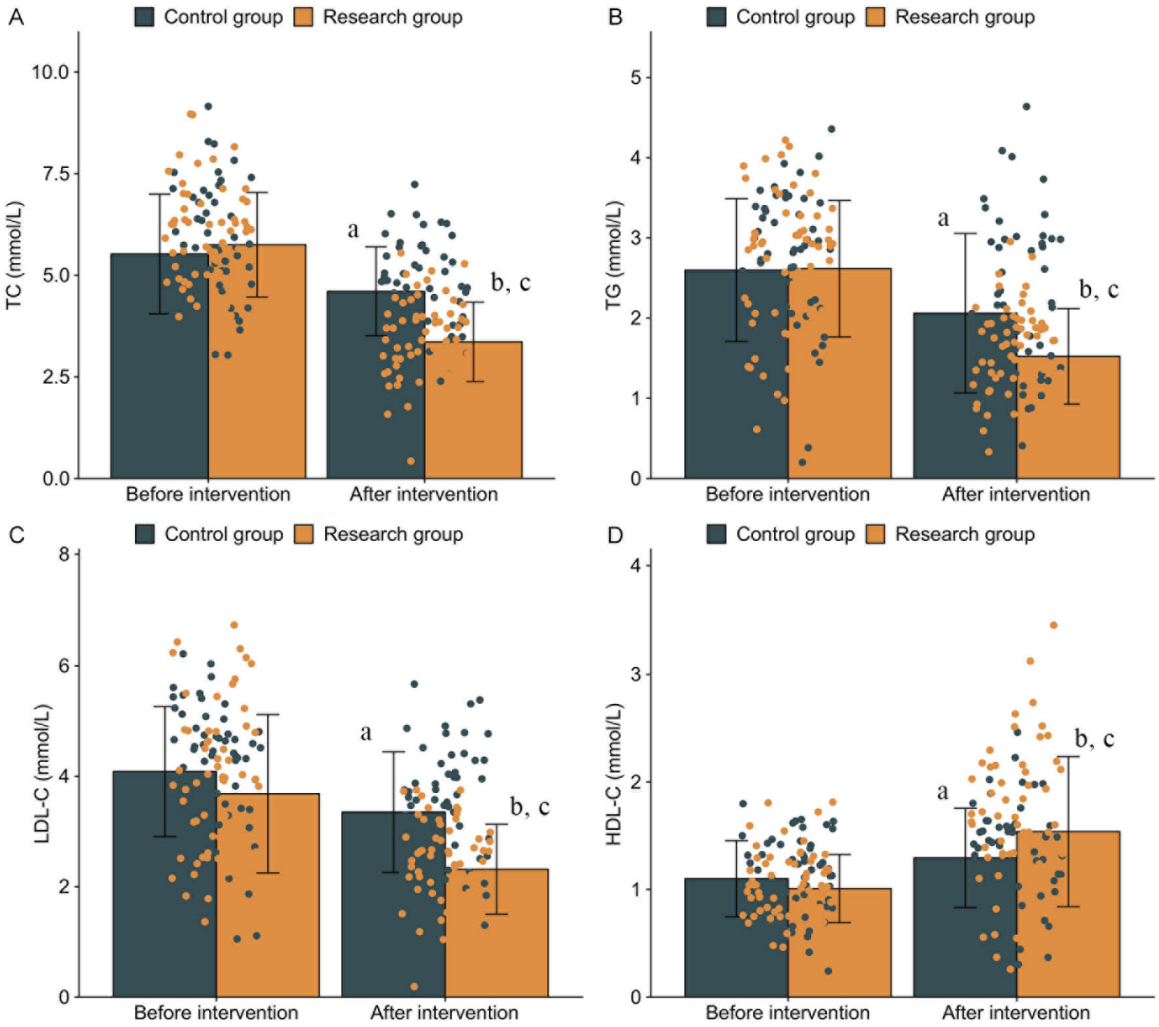

Figure 1. Comparison of blood lipid levels between the two groups before and after treatment. A. TC concentrations; B. TG contents; C. LDL-C levels; D. HDL-C levels. Note: TC, total cholesterol; TG, triglycerides; low/high-density lipoprotein cholesterol (LDL-C/HDL-C). a P<0.05, and b P<0.01, compared with pre-intervention levels; c P<0.05, compared with control group.

Hcy and vascular endothelial function

Figure 2 outlines the alterations in Hcy and endothelial markers (ET-1, NO). Baseline measurements revealed no significant intergroup disparities (P>0.05). Post-intervention, both groups demonstrated declines in Hcy and ET-1 and a rise in NO (P<0.05). Notably, the research group achieved more substantial improvements, characterized by significantly reduced Hcy and ET-1 levels and elevated NO levels (P<0.05).

Serum inflammatory indicators

Figure 3 illustrates changes in IL-6, IL-8, and hs-CRP. No significant baseline differences were observed between groups (P>0.05). Following intervention, both groups demonstrated significant reductions in these inflammatory biomarkers, with the research group displaying more substantial decreases (P<0.05).

Hemorheological parameters

Figure 4 outlines the alterations in hemorheological parameters (HCT, PV, and PAR) for both groups. Pretreatment measurements revealed no significant intergroup differences (P>0.05). Post-intervention, all three parameters improved significantly in both groups (P<0.05), with the research group exhibiting superior enhancements in HCT, PV, and PAR compared with the control group (P<0.05).

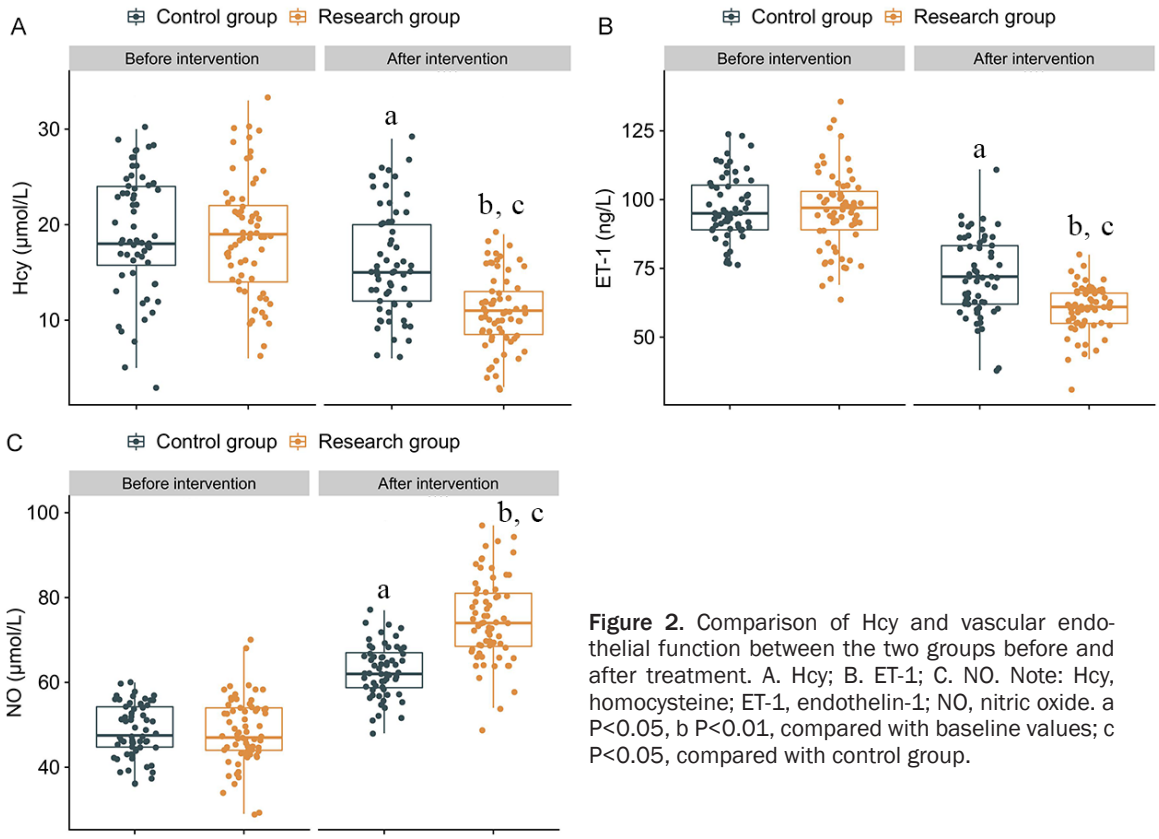

Figure 2. Comparison of Hcy and vascular endothelial function between the two groups before and after treatment. A. Hcy; B. ET-1; C. NO. Note: Hcy, homocysteine; ET-1, endothelin-1; NO, nitric oxide. a $P<0.05$, b $P<0.01$, compared with baseline values; c $P<0.05$, compared with control group.

Discussion

In recent years, the prevalence of HTHT has risen steadily, driven by socioeconomic development, shifts in dietary habits and lifestyles, and an aging population [16]. Clinical evidence indicates that individuals with HTHT are at a substantially higher risk of cardiovascular complications than those with essential hypertension. Their risk of cardiovascular events is approximately 30-fold higher, while the risk of stroke increases by 12-fold [17]. Without prompt intervention, these patients are prone to cerebrovascular dysfunction, brain tissue damage, and metabolic disorders, potentially leading to cognitive deterioration and severe health consequences [18]. Thus, identifying more effective therapeutic strategies is of great clinical significance.

The present study demonstrated that EM-FA tablets enhanced the overall treatment effectiveness rate from 76.67% to 92.54% compared to EM monotherapy, alongside notable reductions in SBP, DBP, and Hcy levels. Liang X et al. [19] reported that the efficacy of this formulation may be associated with the activation of peroxisome proliferator-activated receptor gamma (PPARG). Experimental studies in HTHT mouse models further support these findings, showing that this dual-component formulation mitigates endoplasmic reticulum stress in vascular smooth muscle cells, alleviates vascular damage, reduces Hcy levels, decreases arterial wall thickness, and promotes vascular remodeling, thereby contributing to its therapeutic benefits [20].

In addition, the EM-FA regimen markedly reduced the incidence of stroke (from 11.67% to 1.49%), aligning with the results of Chi X et al. [21] on primary stroke prevention. Supplementation with FA has also been shown to lower the recurrence of atrial fibrillation in HTHT patients undergoing radiofrequency ablation [22]. Further evidence from Liu M et al. [23] indicates that this approach effectively decreases plasma Hcy concentrations while substantially lowering the occurrence of cardiovascular events, supporting our findings.

Regarding safety, EM-FA tablets exhibited excellent tolerability, reducing DRAEs from

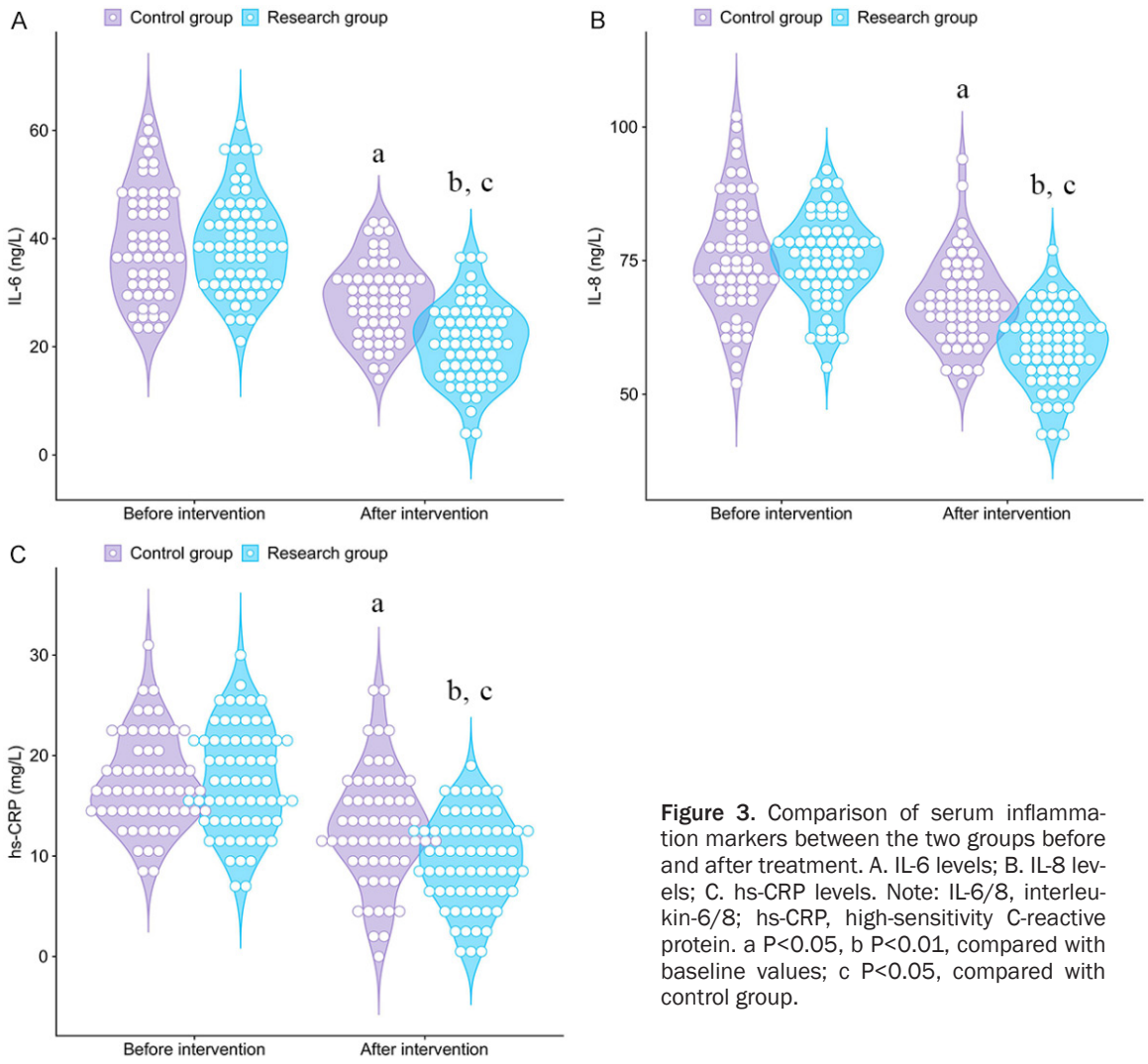

Figure 3. Comparison of serum inflammation markers between the two groups before and after treatment. A. IL-6 levels; B. IL-8 levels; C. hs-CRP levels. Note: IL-6/8, interleukin-6/8; hs-CRP, high-sensitivity C-reactive protein. a P<0.05, b P<0.01, compared with baseline values; c P<0.05, compared with control group.

25.00% to 8.96%. It also showed notable benefits in lipid regulation and endothelial function, as evidenced by reduced ET-1 and elevated NO levels. Preclinical trials [24] further support these findings, showing that FA combined with amlodipine outperforms amlodipine monotherapy in lowering blood pressure and Hcy, while enhancing vascular endothelial function. These findings offer a plausible mechanistic basis for the observed vascular protective benefits in patients with HTHT by EM-FA Tablets.

Our study also confirmed that EM-FA therapy effectively alleviated inflammation and optimized hemorheological parameters. Our experimental data demonstrate that this treatment significantly reduced pro-inflammatory cytokines, including IL-6/8 and hs-CRP, while also enhancing blood fluidity by improving HCT, PV, and PAR. The antihypertensive mechanism involves multifaceted arterial anti-inflammatory and vascular protective actions: (1) reduction of HHcy-related tissue toxicity by lowering Hcy levels; (2) suppression of the nuclear factor κB (NF-κB) p65/Rela/IL-6 pathway to attenuate inflammation; and (3) activation of antioxidant stress pathway molecules to counteract oxidative stress. These synergistic effects collectively ameliorate systemic inflammation in HTHT [25]. Furthermore, a cost-benefit analysis [26] revealed that EM-FA therapy is economically advantageous to EM monotherapy for primary stroke prevention, with 74.5% of simulations favoring its cost-effectiveness.

This study has several limitations. First, the single-center design may limit the generalizability of the findings; future multicenter studies

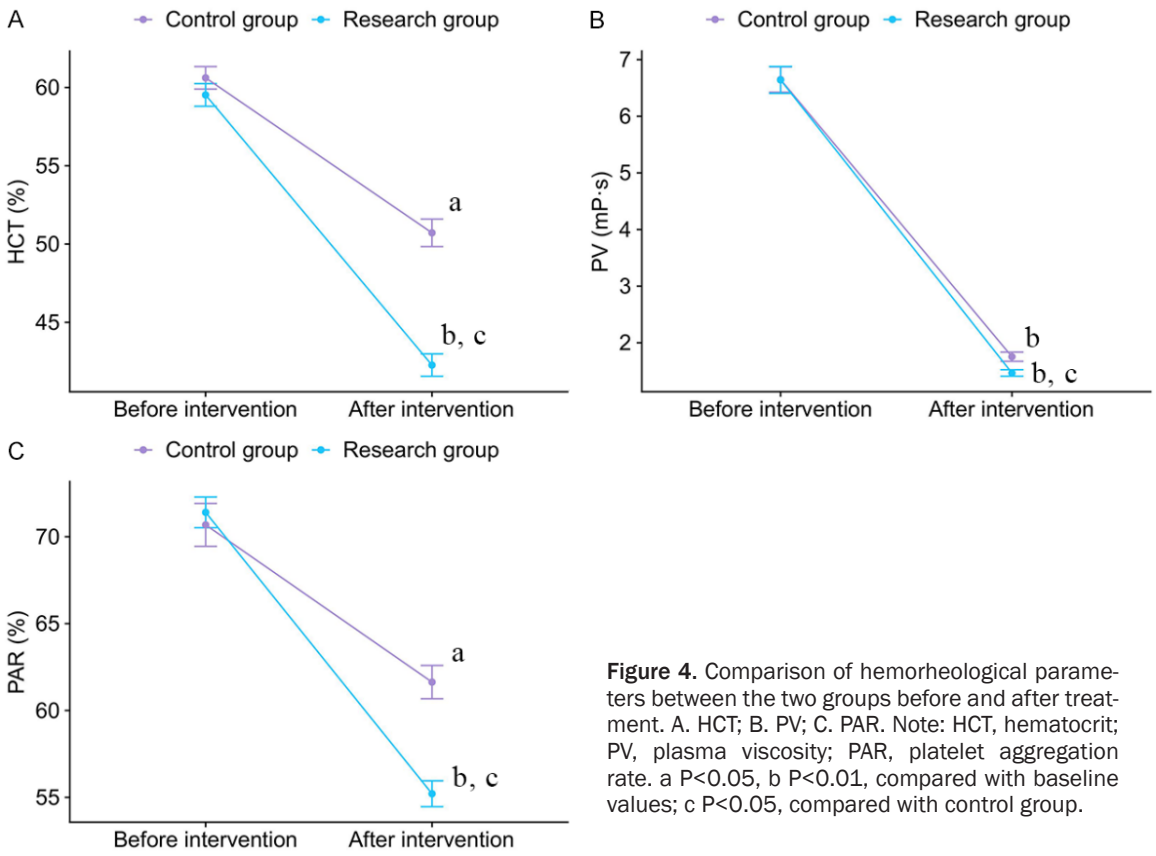

Figure 4. Comparison of hemorheological parameters between the two groups before and after treatment. A. HCT; B. PV; C. PAR. Note: HCT, hematocrit; PV, plasma viscosity; PAR, platelet aggregation rate. a P<0.05, b P<0.01, compared with baseline values; c P<0.05, compared with control group.

with larger sample sizes are warranted to enhance external validity. Second, mechanistic studies are needed to explore the pharmacological pathways underlying EM-FA therapy in HTHT. Third, a comprehensive economic assessment, including long-term healthcare expenditures, insurance implications, and patient affordability would offer a more comprehensive evaluation of the treatment strategies.

In conclusion, EM-FA tablets are highly effective in managing HTHT. Beyond its synergistic effects on blood pressure and Hcy reduction, this therapy is well tolerated and associated with minimal adverse effects. Additionally, it positively influences lipid metabolism, vascular endothelial function, serum inflammation, and hemorheological parameters, supporting its broad clinical utility.

Disclosure of conflict of interest

None.

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