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Original Article

Amlodipine Besylate-Folic Acid demonstrates superior efficacy to Enalapril Maleate-Folic Acid in treating H-type hypertension

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Abstract: Objective: This retrospective research was designed to compare the treatment outcomes of H-type hypertension (HTH) patients treated with Amlodipine Besylate-Folic Acid Tablets (Amlo-FA) vs. Enalapril Maleate-Folic Acid Tablets (Ena-FA). Methods: This investigation comprised 155 HTH cases. The control group was treated with the Ena-FA regimen, while the observation group received Amlo-FA therapy. Patients' clinical data were comparatively analyzed. Results: Compared to controls, the observation group demonstrated superior overall treatment effectiveness (90.48% vs. 71.83%, P=0.003). Following treatment, systolic blood pressure (SBP; (129.86±6.24) mmHg vs. (139.66±8.04) mmHg, P<0.001), diastolic blood pressure (DBP; (80.26±7.46) mmHg vs. (89.00±9.68) mmHg, P<0.001), homocysteine (Hcy; (13.06±3.18) μmol/L vs. (19.39±3.37) μmol/L, P<0.001), carotid intima-media thickness (CIMT; (1.11±0.28) mm vs. (1.29±0.27) mm, P<0.001), fasting blood glucose (FPG; (5.74±1.68) mmol/L vs. (6.40±2.02) mmol/L, P=0.028), glycosylated hemoglobin (HbA1c; (5.85±1.85)% vs. (6.93±1.90)%, P<0.001), urinary albumin-to-creatinine ratio (UACR; (53.64±15.44) mg/L vs. (74.17±16.96) mg/L, P<0.001), total cholesterol (TC; (4.92±1.61) mmol/L vs. (6.42±1.63) mmol/L, P<0.001), TG (triglycerides; (1.66±0.72) mmol/L vs. (2.44±0.68) mmol/L, P<0.001), and low-density lipoprotein cholesterol (LDL-C; (2.35±0.70) mmol/L vs. (2.99±0.84) mmol/L, P<0.001) were markedly reduced in the observation cohort relative to the control group outcomes. Conversely, high-density lipoprotein cholesterol (HDL-C; (1.78±0.69) mmol/L vs. (1.47±0.50) mmol/L, P=0.002), Medication Adherence Self-Efficacy Scale (MASES; (89.31±8.87) score vs. (79.70±7.61) score, P<0.001), and the 8-item Morisky Medication Adherence Scale (MMAS-8; 5.00 (3.00, 6.00) score vs. 6.00 (4.00, 7.00) score, P<0.001) scores showed a significant increase under the same comparisons. The overall side effect profile was significantly more favorable in the observation group (5.95% vs. 16.90%, P=0.030). No significant inter-group differences were observed in the incidence of various individual and total adverse cardiovascular and cerebrovascular events (4.76% vs. 12.68%, P>0.05). Finally, comorbid diabetes (B=1.447, OR=4.250, P=0.010) and treatment methods (B=-1.196, OR=0.303, P=0.013) were factors independently influencing patients' curative effects. Conclusion: Amlo-FA is effective in treating HTH.

Keywords: H-type hypertension, Amlodipine Besylate-Folic Acid Tablets, Enalapril Maleate-Folic Acid Tablets, therapeutic outcomes, blood pressure, lipid metabolism

Introduction

Hypertension is a key risk factor for cardiovascular disease (CVD), with features of preventability and high prevalence [1, 2]. It is defined as having a systolic blood pressure (SBP) of ≥140 mmHg, a diastolic blood pressure (DBP) of ≥90 mmHg, or being on antihypertensive medication. Up to 80% of hypertension cases fall into the category of H-type hypertension (HTH) [3], a condition characterized by elevated homocysteine (Hcy) levels (≥10 μmol/L, known as hyperhomocysteinemia [HHcy]) alongside hypertension [4]. Factors like abnormal Hcy metabolic pathways, dietary methionine intake, and deficiencies in folic acid (FA) and vitamins riboflavin (B2), pyridoxine (B6), and cobalamin (B12) have been identified to trigger Hcy overproduction, which in turn may raise the risk of developing HTH [5]. Furthermore, compared to individuals with simple hypertension, those with HTH face a 30-fold increase in CVD risk and roughly

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a 12-fold higher risk of stroke [6]. This patient group also often exhibits glycolipid metabolic disorders. This is associated with a chronic inflammation-driven imbalance in the inflammatory microenvironment and concomitant insulin sensitivity dysfunction [7]. The main objective in treating HTH is to lower Hcy levels. Clinically, a common practice is to combine antihypertensive drugs with FA to achieve the best possible treatment results [8]. Recent research has shown that sufficient FA supplementation helps reduce serum Hcy concentrations and lessens the influence of genetic predispositions on Hcy levels [9]. Enalapril Maleate-Folic Acid Tablets (Ena-FA), which contain enalapril maleate and FA, can halt disease progression by easing endoplasmic reticulum stress and vascular damage, lowering Hcy levels and carotid intima-media thickness (CIMT), and improving vascular remodeling [10]. In contrast, Amlodipine Besylate-Folic Acid Tablets (Amlo-FA), composed of amlodipine besylate and FA, have been found to be more effective than Amlodipine Besylate alone. They are a safe and effective treatment option for preventing HHcy and supporting blood pressure (BP) control [11].

A paucity of clinical studies exists that directly compare the efficacy of these two agents in treating HTH. This study was therefore conducted to perform a detailed analysis and evaluation on this subject. The innovation of this study lies in the comparative analysis of the clinical effects of Amlo-FA vs. Ena-FA in HTH treatment, which can provide better treatment options for patients. Secondly, we comprehensively evaluated the clinical outcomes of the two treatment schemes from the aspects of curative effects, BP control, Hcy, CIMT, blood sugar control, lipid metabolism, medication self-efficacy/adherence, and adverse drug reactions, confirming the clinical advantages of Amlo-FA in treating HTH patients. Finally, we assessed the effects of the two therapies on adverse cardiovascular and cerebrovascular events. Although the effect of Amlo-FA on cardio-cerebrovascular adverse events was similar to that of Ena-FA, the risk can be controlled at 4.76%, which can provide a more comprehensive reference for the clinical medication decision-making of patients with HTH.

Information and methods

Patient selection

This study adopts a retrospective design. Eligibility for inclusion required: a confirmed HTH diagnosis [12]; age: 18-80; availability of complete medical records; no prior treatment for the condition; no drug contraindications; intact cognition and communication abilities; normal renal function. Exclusion criteria encompassed: aortic valve stenosis; pregnancy or breastfeeding; thyroid dysfunction; concurrent use of anticonvulsants, folate antagonists, hypolipidemics, etc.; current or recent (within 3 months) supplementation with FA or vitamin B; hypersensitivity to study medication; secondary hypertension; severe major organ impairments (liver, kidneys, heart, etc.); psychiatric illness; malignant tumors; infectious diseases; inability to care for oneself; severe impairments in hearing, limb movement and other functions; proteinuria caused by primary kidney disease and diabetes; hematological diseases or hypertensive crisis; hyperkalemia. Following approval from the Huili People's Hospital Ethics Committee, we enrolled 155 HTH patients from Huili People's Hospital who met the strict study criteria. The enrollment period spanned from February 2022 to February 2024. The therapeutic intervention consisted of Ena-FA for the 71 control subjects and Amlo-FA for the 84 individuals in the observation group. The two groups were comparable at baseline with no significant differences in general data ($P>0.05$). Patients' clinical data were retrieved through the case inquiry system. A flow chart of the patient screening process can be seen in **Figure 1**.

Medication methods

All patients received standardized medication and exercise guidance, with adjustments made according to their individual conditions. On this basis, the pharmacological regimen involved a once-daily oral tablet of either Ena-FA (composition per tablet: 10 mg enalapril maleate/0.8 mg FA) for the control group or Amlo-FA (composition per tablet: 5 mg amlodipine besylate [calculated by amlodipine] and 0.8 mg FA) for the observation group. Both groups underwent a 6-month treatment course. The treatment pl-

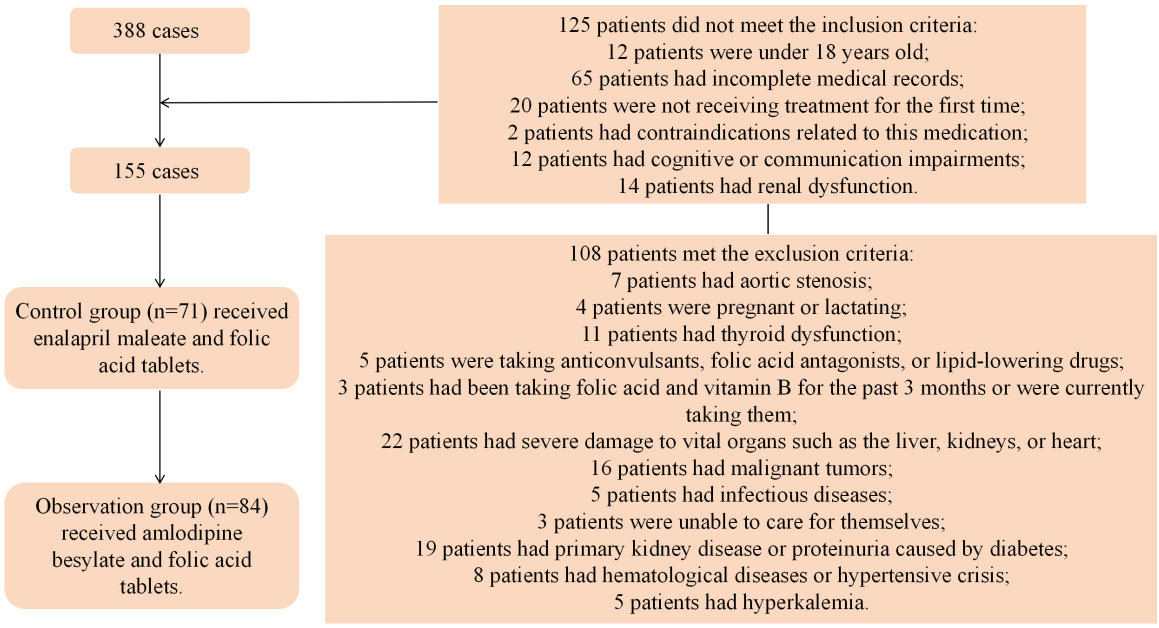

Figure 1. Flowchart of the patient screening process.

ans, rather than randomly assigned, were comprehensively decided by the attending physician according to the patient's clinical characteristics, complications, and drug indications. All patients were fully informed of the potential benefits and risks of the two schemes before treatment.

Data extraction

The following indicators were extracted and verified by the case inquiry system:

(1) Efficacy [13]. Curative effect evaluation criteria: Significantly effective: BP normalization (SBP 90-139 mmHg, DBP 60-89 mmHg; 1 mmHg=0.133 kPa) plus Hcy reduction to ≤10 μmol/L; Effective: A reduction in DBP of >10 mmHg (non-normalized) plus a >25% decrease in Hcy levels; Ineffective: Failure to meet the criteria for either "Significantly effective" or "Effective". The total effective rate was calculated as the proportion of cases categorized as either "Significantly effective" or "Effective" out of the total number of cases.

(2) BP control. Pre- and post-medication SBP and DBP were assessed for all subjects using an upper arm electronic sphygmomanometer.

(3) Serum biochemical indices. Fasting venous blood samples (6 mL) were drawn pre- and post-intervention. Serum, isolated through centrifugation, was analyzed for Hcy concentration on an automated analyzer using a cyclic enzyme Method assay. Meanwhile, CIMT measurements were taken at the common carotid artery bifurcation using high-frequency vascular ultrasound.

(4) Blood sugar control. Glycemic control was evaluated by measuring fasting blood glucose (FPG), glycosylated hemoglobin (HbA1c), and the urinary albumin-to-creatinine ratio (UACR). An automatic biochemical analyzer was used to quantify these parameters at baseline and after the course of drug administration.

(5) Lipid metabolism. We measured pre- and post-treatment total cholesterol (TC), triglyceride (TG), and low-/high-density lipoprotein cholesterol (LDL-C/HDL-C) in patients' serum using an automatic biochemical detector.

(6) Medication self-efficacy and adherence [14]. To gauge patients' self-efficiency in taking their medication, the study employed the Medication Adherence Self-Efficacy Scale (MASES). Comprising 26 items, each rated on a 4-point Likert scale (from 1 to 4 points), the scale has a maximum achievable score of 104. A higher result is interpreted as stronger self-efficacy. The scale's Cronbach's α coefficient is 0.841. The Morisky Medication Adherence Scale-8 (MMAS-8) assessed adherence through 8 items: 7 binary (Yes/No, 1/0 point) and 1 on a 5-point Likert scale (options: 0, 0.25,

Table 1. General information of the control and observation groups

Data	Control group (n=71)	Observation group (n=84)	χ^2/Z/t	P
Average age (years)	52.25±6.67	52.49±7.13	0.215	0.830
Male	45 (63.38)	48 (57.14)	0.624	0.430
Hypertensive history (months)	4.00 (1.00, 7.00)	4.00 (2.00, 9.00)	-1.116	0.264
Body mass index (kg/m^2)	25.00 (23.00, 27.00)	25.00 (22.00, 27.00)	-0.182	0.855
Diabetes	6 (8.45)	15 (17.86)	2.907	0.088
Hyperlipidaemia	10 (14.08)	19 (22.62)	1.843	0.175
Chronic kidney disease	0 (0.00)	3 (3.57)	-	0.250
Family medical history	7 (9.86)	7 (8.33)	0.109	0.741

Note: The χ^2 test is used to evaluate between-group differences for counting data, such as male and diabetes. The independent sample t-test is used to analyze inter-group differences for measurement data like average age and hypertensive history; *P*-values less than 0.05 indicate the presence of statistically significant differences between groups.

0.50, 0.75, 1.00). The aggregate score, which can reach 8 points, is directly proportional to adherence levels. The scale's Cronbach's α is 0.83.

(7) Medication-related side effects. Patients were monitored for the occurrence of treatment-emergent adverse events like renal dysfunction, angioneurotic edema, cough, and headache following the treatment. The overall incidence rate was then calculated.

(8) Adverse cardiovascular and cerebrovascular events. Post-treatment occurrences of myocardial infarction, stroke, and cardiocerebrovascular mortality were tracked. The overall incidence of these outcomes was computed.

Outcome measures

In this study, the general data (average age, male, disease course, BMI, diabetes, hyperlipidemia, chronic kidney disease, and family medical history), clinical efficacy, BP control, Hcy/CIMT, blood sugar control, lipid metabolism, medication self-efficacy/adherence, medication-related side effects, and adverse cardiovascular and cerebrovascular events of both the observation and control groups were obtained to verify whether Amlo-FA has a more significant clinical advantage in HTH treatment. Of various measures, clinical efficacy, BP control, Hcy/CIMT, medication self-efficacy/adherence, medication-related side effects, and adverse cardiovascular and cerebrovascular events are primary, while general information, blood sugar control, and lipid metabolism are secondary.

Statistical methods

Continuous variables were first subjected to Bartlett's test for variance homogeneity and the Shapiro-Wilk test for normality. If variance homogeneity and approximately normal distribution were satisfied, the data were presented as the mean ± standard deviation, with inter-group comparisons performed using independent sample t-tests and intra-group comparisons conducted with paired sample t-tests; if not fulfilled, they were expressed as the median (interquartile range), and comparisons between groups and within groups (pre- vs. post-intervention) were conducted using the Mann-Whitney U test and the Wilcoxon signed-rank test, respectively. Categorical variables, expressed by the number of cases (percentages), were analyzed by the chi-square test or Fisher's exact test (when the theoretical frequency is less than 5). Uni- and multi-variate (binary logistic regression) analyses were conducted to identify efficacy-associated determinants. SPSS 26.0 and GraphPad Prism 7.0 were utilized for data analysis and figure plotting/exportation, respectively. A significance threshold of $P<0.05$ was employed for all tests.

Results

General data

As detailed in **Table 1**, the control and observation groups possessed comparable baseline characteristics. All measured variables, including mean age, male proportion, hypertensive history, body mass index (BMI), diabetic status, hyperlipidaemia, chronic kidney disease, and family medical history showed no statistically notable differences ($P>0.05$), confirming their feasibility for comparison.

Clinical efficacy

We compared the clinical outcomes for both groups, with the results presented in **Table 2**.

Table 2. Clinical efficacy of control and observation groups

Indicators	Control group (n=71)	Observation group (n=84)	χ^2	P
Significantly effective	28 (39.44)	48 (57.14)		
Effective	23 (32.39)	28 (33.33)		
Ineffective	20 (28.17)	8 (9.52)		
Overall effectiveness	51 (71.83)	76 (90.48)	9.037	0.003

Note: The inter-group differences of the two sets of count data were evaluated using the χ^2 test; a *P* value less than 0.05 indicates that there is a statistically significant difference between the groups.

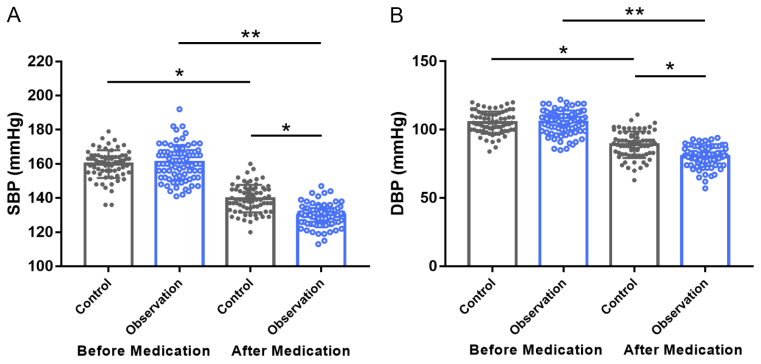

Figure 2. BP control in control group and observation group. A. SBP alterations before and after medication. B. DBP changes before and after medication. Note: SBP/DBP, systolic/diastolic blood pressure. *P<0.05; **P<0.01. The independent sample t-test and paired t-test are used to analyze between-group differences (at the same time point) and within-group differences (pre- vs. post-treatment) of measurement data, respectively; P<0.05 indicates the presence of statistically significant differences.

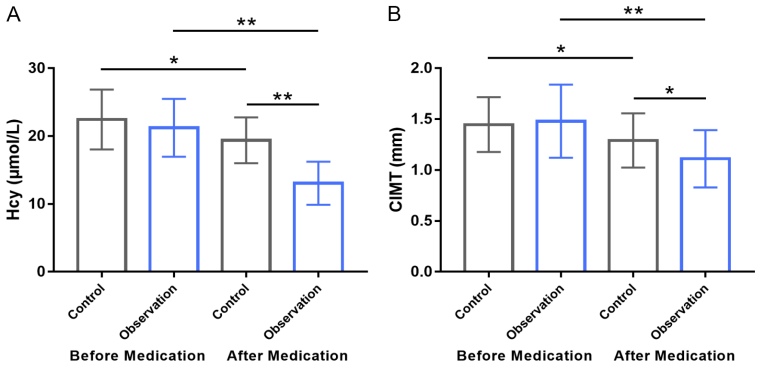

Figure 3. Hcy and CIMT measurements in the study cohorts. A. Hcy changes pre- and post-treatment. B. CIMT alterations level pre- and post-medication. Note: Hcy, homocysteine; CIMT, carotid intima-media thickness. *P<0.05; **P<0.01. The independent sample t-test is used to analyze the differences between groups in the measurement data at the same time point, while the paired t-test is employed to evaluate the differences before and after treatment within the same group; *P*-values <0.05 indicate that there are differences in the comparison between the groups.

The total effective rate reached 90.48% in the observation group, markedly surpassing the rate of 71.83% achieved in the control group (P<0.01).

BP control

The efficacy of BP control is illustrated in **Figure 2**. Baseline SBP and DBP showed no significant intergroup difference (P>0.05). Following treatment, however, both indices markedly decreased in all patients (P<0.05). Notably, the post-medication levels of SBP and DBP were significantly lower in the observation group compared to controls (P< 0.05).

Hcy and CIMT

As illustrated in **Figure 3**, no significant intergroup differences in Hcy or CIMT were observed prior to treatment (P> 0.05). Therapeutic intervention resulted in a pronounced decline in both biomarkers within each group (P<0.05). According to the inter-group comparison, the observation group demonstrated greater Hcy and CIMT reductions relative to the control group (P< 0.05).

BG control

The glycemic control outcomes for both cohorts are presented in **Table 3**. At baseline, the groups had similar FPG, HbA1c, and UACR values (P>0.05). Post-treatment, the control group exhibited a marked reduction in FPG and UACR (P<0.05), whereas the change in HbA1c was not significant (P>0.05). Post-treatment FPG,

Table 3. Blood sugar control in control and observation groups

Indicators	Control group (n=71)	Observation group (n=84)	t	P
FPG (mmol/L)				
Before medication	7.28±2.50	7.21±2.31	0.181	0.857
After medication	6.40±2.02	5.74±1.68	2.221	0.028
t	2.307	4.717		
P	0.023	<0.001		
HbA1c (%)				
Before medication	6.57±2.31	7.24±2.49	1.725	0.087
After medication	6.93±1.90	5.85±1.85	3.577	<0.001
t	1.014	4.107		
P	0.312	<0.001		
UACR (mg/L)				
Before medication	114.96±19.14	117.45±20.16	0.784	0.434
After medication	74.17±16.96	53.64±15.44	7.884	<0.001
t	13.440	23.031		
P	<0.001	<0.001		

Note: FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; UACR, urinary albumin-to-creatinine ratio. For measurement data, the independent sample t-test and paired t-test are used to analyze between-group differences (at the same time point) and within-group differences (pre- vs. post-treatment), respectively; P<0.05 indicates the existence of statistically significant differences.

Table 4. Lipid metabolism across the cohorts

Indicators	Control group (n=71)	Observation group (n=84)	t	P
TC (mmol/L)				
Before medication	7.73±1.91	7.87±1.84	0.464	0.643
After medication	6.42±1.63	4.92±1.61	5.746	<0.001
t	4.396	11.059		
P	<0.001	<0.001		
TG (mmol/L)				
Before medication	3.33±1.17	3.09±1.22	1.243	0.216
After medication	2.44±0.68	1.66±0.72	6.892	<0.001
t	5.542	9.252		
P	<0.001	<0.001		
LDL-C (mmol/L)				
Before medication	4.17±1.53	4.15±1.25	0.090	0.929
After medication	2.99±0.84	2.35±0.70	5.174	<0.001
t	5.697	11.515		
P	<0.001	<0.001		
HDL-C (mmol/L)				
Before medication	1.23±0.42	1.21±0.31	0.340	0.734
After medication	1.47±0.50	1.78±0.69	3.150	0.002
t	3.097	6.906		
P	0.002	<0.001		

Note: TC, total cholesterol; TG, triglyceride; LDL-C/HDL-C, low-/high-density lipoprotein cholesterol. The independent sample t-test is used to analyze the differences between groups in the measurement data at the same time point, while the paired t-test is employed to evaluate the differences before and after treatment within the same group; *P*-values <0.05 indicate that there are differences in the comparison between the groups.

HbA1c, and UACR were reduced to a greater extent in the observation group, ultimately falling below the levels seen in the control subjects (P<0.05).

Table 5. Medication self-efficacy and adherence in both cohorts

Indicators	Control group (n=71)	Observation group (n=84)	t/Z	P
MASES (points)				
Before medication	77.54±6.12	76.11±7.60	1.274	0.205
After medication	79.70±7.61	88.95±8.35	7.154	<0.001
t	1.864	10.423		
P	0.065	<0.001		
MMAS-8 (points)				
Before medication	4.00 (3.00, 5.00)	4.00 (3.00, 5.00)	-0.448	0.654
After medication	5.00 (3.00, 6.00)	6.00 (4.00, 7.00)	-3.214	0.001
Z	-2.227	-5.661		
P	0.026	<0.001		

Note: MASES, Medication Adherence Self-Efficacy Scale; MMAS-8, Morisky Medication Adherence Scale-8. The independent sample t-test and paired t-test are used to analyze between-group differences (at the same time point) and within-group differences (pre- vs. post-treatment) of measurement data, respectively; P<0.05 indicates the presence of statistically significant differences.

Table 6. Side effects of medication in control and observation groups

Indicators	Control group (n=71)	Observation group (n=84)	χ^2	P
Renal dysfunction	2 (2.82)	0 (0.00)		
Angioneurotic edema	1 (1.41)	0 (0.00)		
Cough	6 (8.45)	2 (2.38)		
Headache	3 (4.23)	3 (3.57)		
Total	12 (16.90)	5 (5.95)	4.724	0.030

Note: The χ^2 test is used to assess between-group differences for count data; a *P* value less than 0.05 indicates that there are differences between the groups.

Lipid metabolism

The lipid metabolic parameters for both groups are detailed in **Table 4**. Initially, serum TC, TG, LDL-C, and HDL-C showed no significant inter-group disparity (P>0.05). Post-therapy, significant improvements in all lipid parameters were observed in both cohorts, characterized by decreases in TC, TG, and LDL-C and an increase in HDL-C (P<0.05). However, the improvements in the observation group were more pronounced, with final values for TC, TG, and LDL-C being substantially lower and HDL-C being higher than those achieved in controls (P<0.05).

Medication self-efficacy and adherence

As shown in **Table 5**, initial MASES and MMAS-8 scores showed no inter-group disparity (P> 0.05). Post-intervention, the control group's MASES remained unchanged, while its MMAS-8 improved significantly from baseline (P< 0.05). The observation group, however, displayed post-treatment scores significantly surpassing those of the control group for both assessment tools (P<0.05).

Medication-related side effects

Medication-related adverse events were compared between the two groups (**Table 6**). The monitored events were renal dysfunction, angioneurotic edema, cough, and headache. The analysis revealed a statistically significant reduction in the total rate of these events within the observation group compared to the controls (P<0.05).

Adverse cardiovascular and cerebrovascular events

Analysis of adverse cardiovascular and cerebrovascular events (myocardial infarction, stroke, and cardiocerebrovascular mortality) data are compiled in **Table 7**. The total incidence in the observation group (4.76%) was not significantly different from the 12.68% rate observed in the control group (P>0.05).

Table 7. Adverse cardiovascular and cerebrovascular events in control and observation groups

Indicators	Control group (n=71)	Observation group (n=84)	χ^2	P
Myocardial infarction	3 (4.23)	2 (2.38)		
Stroke	4 (5.63)	2 (2.38)		
Cardiocerebrovascular mortality	2 (2.82)	0 (0.00)		
Total	9 (12.68)	4 (4.76)	3.137	0.077

Note: The χ^2 test is employed for between-group comparisons of count data; *P*-values less than 0.05 indicate the presence of statistically significant differences between the groups.

Table 8. Univariate analysis of factors influencing patients' curative effects

Indicators	n	Ineffective group (n=28)	Effective group (n=127)	χ^2/Z/t	P
Age (years)				1.788	0.181
<50	55	13 (46.43)	42 (33.07)		
≥50	100	15 (53.57)	85 (66.93)		
Sex				0.116	0.733
Male	93	16 (57.14)	77 (60.63)		
Female	62	12 (42.86)	50 (39.37)		
Disease course (years)				2.543	0.111
<5	82	11 (39.29)	71 (55.91)		
≥5	73	17 (60.71)	56 (44.09)		
Body mass index (kg/m^2)				0.242	0.623
<25	84	14 (50.00)	70 (55.12)		
≥25	71	14 (50.00)	57 (44.88)		
Diabetes	21	9 (32.14)	12 (9.45)	10.088	0.002
Hyperlipidaemia	29	10 (35.71)	19 (14.96)	6.497	0.011
Chronic kidney disease	3	2 (7.14)	1 (0.79)	-	0.084
Family medical history	14	5 (17.86)	9 (7.09)	3.239	0.072
Treatment modality				9.037	0.003
Enalapril Maleate-Folic Acid Tablets	71	20 (71.43)	51 (40.16)		
Amlodipine Besylate-Folic Acid Tablets	84	8 (28.57)	76 (59.84)		
SBP (mmHg)	155	159.93±7.98	160.50±9.54	0.294	0.769
DBP (mmHg)	155	106.43±8.43	105.15±8.28	0.738	0.462
Hcy (μmol/L)	155	20.82±4.09	22.00±4.40	1.300	0.196
CIMT (mm)	155	1.41±0.34	1.48±0.32	1.036	0.302
FPG (mmol/L)	155	7.27±2.63	7.24±2.35	0.060	0.952
HbA1c (%)	155	6.94±2.29	6.93±2.46	0.020	0.984
UACR (mg/L)	155	112.64±15.76	117.12±20.40	1.091	0.277
TC (mmol/L)	155	8.10±1.91	7.74±1.86	0.923	0.358
TG (mmol/L)	155	3.26±1.23	3.19±1.20	0.278	0.781
LDL-C (mmol/L)	155	4.72±1.58	4.03±1.31	2.427	0.016
HDL-C (mmol/L)	155	1.29±0.42	1.21±0.35	1.055	0.293
MASES (points)	155	76.93±6.76	76.72±7.05	0.144	0.886
MMAS-8 (points)	155	3.00 (3.00, 6.00)	4.00 (3.00, 5.00)	-0.136	0.892

Note: SBP/DBP, systolic/diastolic blood pressure; Hcy, homocysteine; CIMT, carotid intima-media thickness; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; UACR, urinary albumin-to-creatinine ratio; TC, total cholesterol; TG, triglyceride; LDL-C/HDL-C, low-/high-density lipoprotein cholesterol; MASES, Medication Adherence Self-Efficacy Scale; MMAS-8, Morisky Medication Adherence Scale-8.

Table 9. Efficacy-associated determinants by multivariate analysis

Indicators	B	Standard error	Wald	P	OR	95% CI
Diabetes	1.447	0.558	6.722	0.010	4.250	1.423-12.689
Hyperlipidaemia	0.741	0.517	2.060	0.151	2.099	0.763-5.777
Treatment modality	-1.196	0.482	6.155	0.013	0.303	0.118-0.778
LDL-C (mmol/L)	0.307	0.170	3.289	0.070	1.360	0.975-1.896

Note: LDL-C, low-density lipoprotein cholesterol.

Analysis of factors influencing curative effects

We performed univariate analysis on all potential factors influencing curative effects (**Table 8**). Efficacy was found to be markedly correlated with diabetes, hyperlipidemia, treatment modality, and LDL-C ($P<0.05$), but not with age, sex, disease course, BMI, chronic kidney disease, family medical history, SBP, DBP, Hcy, CIMT, FPG, HbA1c, UACR, TC, TG, HDL-C, MASES, or MMAS-8.

In the further multivariate analysis (**Table 9**), diabetes (B=1.447, OR=4.250) and treatment modality (B=-1.196, OR=0.303) were confirmed as factors independently impacting patients' curative effects ($P<0.05$), but not hyperlipidaemia or LDL-C ($P>0.05$).

Discussion

Affecting roughly one third of the global population, hypertension is frequently complicated by HHcy, which co-occurs in up to 75% of cases [15, 16]. HTH is a significant risk factor for stroke and coronary heart disease, as it drives the development of atherosclerosis. As the condition progresses, it may further lead to myocardial necrosis, a high-mortality outcome with substantial complication risks that severely jeopardize patient wellbeing [17]. To better curb disease progression, there is an urgent need to optimize therapeutic strategies for individuals diagnosed with HTH.

Currently, the pharmacotherapeutic management of hypertension relies on several drug classes, including calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs), diuretics, and α/β-blockers. Nevertheless, issues like poor compliance and inadequate symptom control often limit their clinical utility [18]. As indicated in prior research, an individualized FA regimen can enhance HTH management: it effectively reduces BP, Hcy levels, and coagulation factors, while concurrently correcting the prethrombotic state. Consequently, FA supplementation adjunctive to antihypertensive medication may potentiate overall antihypertensive efficacy [19]. According to a systematic review [20], FA supplementation elucidates a dose- and duration-dependent effect on BP reduction in hypertension. In the present study, Amlo-FA demonstrates therapeutic efficacy (90.48% versus 71.83%) superior to Ena-FA in HTH. Beyond substantially reducing Hcy and CIMT, Amlo-FA also achieves more favorable BP control outcomes. Amlo-FA and Ena-FA are both FA-based compound preparations. The former incorporates a CCB, renowned for its efficacy in reducing both BP and Hcy levels. Besides, it strengthens vascular endothelial function and offers certain cardioprotective and vasoprotective benefits [21]. Amlodipine besylate has also been indicated to ameliorate hypertension by regulating the intestinal microflora equilibrium [22]. The antihypertensive action of enalapril maleate, an ACEI present in the drug Ena-FA, arises principally from its ability to modulate the renin-angiotensin-aldosterone system [23]. In this study, Amlo-FA has a more significant down-regulation effect on Hcy and CIMT in HTH-affected patients, potentially linked to its more potent BP-lowering action.

Additionally, in terms of glycometabolic and lipid metabolic control, Amlo-FA also demonstrated superiority over Ena-FA. It also shows more prominent advantages in enhancing patients' medication self-efficacy and adherence. This is postulated to be a consequence of its more robust therapeutic outcomes, which encompass better control of hypertension, glycemia, and lipid levels, as well as a reduced rate of total adverse events. The resultant increase in patient confidence in overcoming their disease thereby promotes a more proactive attitude toward medication adherence. Regarding medication-related side effects, Amlo-FA more significantly reduces the incidence of total

adverse events such as renal dysfunction, angioedema, cough, and headache in patients with HTH (5.95% vs. 16.90%) than Ena-FA, despite an equivalent influence on adverse cardiovascular and cerebrovascular events like myocardial infarction, stroke and cardiocerebrovascular mortality (4.76% vs. 12.68%). Ena-FA intervention is associated with a higher overall adverse event rate in HTH patients, potentially because, as an ACEI, it dilates the efferent arteriole more significantly than the afferent arteriole, thereby reducing the glomerular filtration rate. Meanwhile, the similar impact on cardio-cerebrovascular events between groups could be linked to the study's short duration and small cohort. Finally, it was found that diabetes was an independent risk factor for the therapeutic effect of HTH patients, while Amlo-FA treatment was an independent protective factor. This suggests that diabetes will increase the risk of ineffective treatment in HTH patients; conversely, treatment with Amlo-FA helps buffer against this risk.

This study showed room for further refinement: (1) Key determinants of adverse cardiovascular and cerebrovascular events in HTH were not analyzed; in the future, relevant analysis should be supplemented to further determine the key influencing factors in order to formulate targeted preventive measures; (2) There is a lack of analysis of the impact of these two therapies on patients' sleep and quality of life. Supplemental analysis in this aspect can aid in further verifying the potential clinical superiority of Amlo-FA therapy; (3) Given the absence of discussions on treatment cost and economic benefits, conducting such an analysis in the future may help further promote the clinical application of Amlo-FA.

To conclude, patients with HTH should give priority to Amlo-FA instead of Ena-FA. The former leads to superior curative efficacy, curtails disease progression, achieves more effective BP control, and promotes healthier glucolipid metabolism. What's more, it shows higher efficacy in bolstering medication self-efficacy and adherence while minimizing total adverse events. Amlo-FA is therefore an optimal treatment for HTH. Notably, comorbid diabetes can elevate the treatment difficulty of HTH.

Disclosure of conflict of interest

None.

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