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ORIGINAL RESEARCH

Long-Term Benefits of N-Butylphthalide in Preventing Ischemic Stroke Recurrence: A 12-Month Prospective Study

Wei Liu[1,*], Yingzhe Shao[1,*], Jie Liu[2,*], Juan Hao[1], Yuting Lu[3], Li Yang[1], Jinghua Wang[1,4,5], Xianjia Ning[1,4,5]

[1]Department of Neurology, Tianjin Medical University General Hospital, Tianjin, People's Republic of China; [2]Department of Critical Care Medicine, Tianjin Medical University General Hospital, Tianjin, 300052, People's Republic of China; [3]School of Basic medical Sciences, Tianjin Medical University, Tianjin, 300070, People's Republic of China; [4]Laboratory of Epidemiology, Tianjin Neurological Institute, Tianjin, 300052, People's Republic of China; [5]Tianjin Neurological Institute, Key Laboratory of Post-Neuroinjury Neuro-Repair and Regeneration in Central Nervous System, Ministry of Education and Tianjin City, Tianjin, 300052, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xianjia Ning; Jinghua Wang, Department of Neurology, Tianjin Medical University General Hospital, Laboratory of Epidemiology, Tianjin Neurological Institute &Tianjin Neurological Institute, Key Laboratory of Post-Neuroinjury Neuro-repair and Regeneration in Central Nervous System, Ministry of Education and Tianjin City, 154 Anshan Road, Heping District, Tianjin, 300052, People's Republic of China, Tel +86-22-60817505; +86-22-60817504, Fax +86-22-60817448, Email xning@tmu.edu.cn; jwang3@tmu.edu.cn

Purpose: This study evaluated the effects of 12 months of NBP treatment on stroke recurrence and examined the influence of age and gender on its efficacy.

Methods: A prospective cohort of 1109 patients with non-cardioembolic ischemic stroke (IS) within six months was divided into NBP (n = 538) and control (n = 571) groups. The NBP group received NBP plus standard treatment, while the control group received standard treatment alone. Primary outcomes were recurrent ischemic and hemorrhagic stroke over 12 months. Secondary outcomes included functional status (modified Rankin Scale, m-RS) and all-cause mortality.

Results: NBP reduced recurrent IS by 39% compared to controls (RR:0.61,95% CI:0.40–0.93, P=0.022) and total stroke events by 39.6% (RR:0.60,95% CI:0.40–0.91,P=0.016). Protective effects were more significant in males (RR:0.52,95% CI:0.30–0.91, P=0.021 vs RR:0.53,95% CI:0.40–0.91,P=0.021) and in patients under 70 years (P<0.05). Functional outcomes (modified Rankin Scale and Barthel index) and all-cause mortality did not differ significantly between groups (all P>0.05).

Conclusion: NBP significantly reduces stroke recurrence and overall vascular events, especially in males and younger patients. While it does not improve functional outcomes or mortality, NBP demonstrates substantial preventive value for recurrent strokes.

Keywords: N-butylphthalide, ischemic stroke, stroke recurrence, cardiovascular events, secondary prevention

Introduction

Ischemic stroke (IS) is one of the leading causes of death and disability worldwide, imposing a significant burden on healthcare systems and society. In China, the incidence of new stroke cases has risen dramatically, reaching approximately 3.94 million in 2019—an 86% increase compared to 1990.[1] Stroke recurrence poses an even greater challenge, as it is associated with higher rates of morbidity, mortality, and healthcare costs.[2] Despite advances in the acute management of IS, such as antiplatelet therapy and the use of thrombolytic agents, secondary prevention remains a pressing clinical priority.[3–5] In China, the one-year recurrence rate for IS stands at approximately 12.5%, underscoring the urgent need for effective long-term preventive strategies.[6]

Current secondary prevention strategies for IS typically combine pharmacological interventions, including antiplatelet agents, statins, and antihypertensive drugs, with lifestyle modifications. However, despite these measures, some patients continue to experience recurrent strokes, with the five-year risk of recurrence in patients with large artery atherosclerosis

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remaining as high as 20% to 30%.[7] This highlights the need for novel therapeutic options that can effectively reduce stroke recurrence.

N-butylphthalide (NBP), a synthetic compound originally derived from celery seeds, has garnered increasing attention as a neuroprotective agent in the treatment of IS. NBP has demonstrated multiple mechanisms of action, including the preservation of mitochondrial function, the enhancement of cerebral energy metabolism, and the inhibition of neuronal apoptosis.[8–10] These mechanisms make NBP a promising candidate for mitigating the neuronal damage associated with IS. Early clinical trials and meta-analyses have shown that NBP, when used during the acute phase of IS, can reduce neurological deficits and improve functional recovery.[11,12] When administered in conjunction with standard stroke treatments, such as antiplatelet therapy and statins, NBP has been associated with reduced mortality and enhanced functional outcomes.[11,12]

Despite its proven short-term benefits, the long-term effects of NBP on IS recurrence remain inconclusive. Most previous studies have focused on short-term outcomes, with follow-up periods lasting only a few months.[13] Additionally, many of these studies had small sample sizes, limiting their ability to draw robust conclusions regarding the long-term impact of NBP. There is also a paucity of data on whether the efficacy of NBP differs according to patient characteristics, such as age and gender.[14–16] These knowledge gaps have hindered the development of personalized treatment strategies for stroke survivors.

This study aims to address these gaps by investigating the effects of a 12-month regimen of NBP on IS recurrence. Specifically, the study examines the protective effects of NBP against stroke recurrence and evaluates how age and gender may influence its efficacy. We hypothesize that NBP treatment will significantly reduce the recurrence rate of IS, with greater efficacy in male and younger patients.

Methods

Study Design and Setting

This community-based prospective cohort study was conducted in Jizhou District, Tianjin, China. The trial design adhered to the ethical principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Tianjin Medical University General Hospital (IRB2020-YX-056-01). Written informed consent was obtained from all participants prior to their enrollment. The study was registered with the Chinese Clinical Trial Registration Center (ChiCTR2000039118).

Participants

The study enrolled male and female adults aged 18 years and older who were permanent residents of Jizhou District and had been diagnosed with non-cardioembolic IS within the past six months, as confirmed by medical record data and magnetic resonance imaging (MRI). Participants were required to be capable of self-care or have access to a caregiver for assistance. Exclusion criteria included a history of hemorrhagic stroke, the presence of malignant tumors, coagulation disorders (platelets $<100\times10^9$/L), severe hepatic or renal dysfunction, cardiac dysfunction, pregnancy, and concurrent participation in other clinical trials. Patients with severe cognitive impairment or those unable to provide informed consent were also excluded from the study.

Intervention

Participants were recruited and assigned to one of two groups using a 1:1 cluster sampling ratio in two phases. In the first phase, eligible participants who met the inclusion criteria were enrolled in the NBP treatment group between April and July 2021. In the second phase, from October 2021 to March 2022, eligible participants meeting the selection criteria were assigned to the control group. The NBP group received NBP soft capsules at a dosage of 0.2 g, administered three times daily for 12 months, in addition to standard treatment. Studies have shown that this dose of NBP therapeutic regimen shows good efficacy and safety.[17–20] Standard treatment included a regimen of antiplatelet agents, antihypertensive medications, antidiabetic drugs, or lipid-lowering agents, based on the individual's clinical requirements. However, the standard treatment plan of all patients followed the authoritative domestic and foreign guidelines for

secondary prevention of IS. Participants in the control group continued to receive standard treatment alone, without the addition of NBP. To ensure medication compliance, we provide detailed medication guidance. All NBP patients were first given drugs for one month after enrollment, then given drugs every three months, and the empty bottles were recovered at the same time. The medication compliance reached more than 80%.

Baseline Data Collection

Baseline data were collected for all participants at the time of enrollment. The collected information included demographic characteristics (age, gender, body mass index), medical history (including the presence of hypertension, diabetes, hyperlipidemia, and coronary artery disease), and lifestyle factors (such as smoking status and alcohol consumption). Biochemical markers relevant to stroke risk were also measured. After a fasting period of at least 12 hours, venous blood samples were drawn to assess levels of glycated hemoglobin, homocysteine, high-sensitivity C-reactive protein (hs-CRP), total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Baseline functional status was assessed using the modified Rankin Scale (m-RS) and Barthel index, which served as a reference point for subsequent functional outcome evaluations.

Follow-Up and Outcome Measures

Participants were followed up for a 12-month period. The primary outcomes of interest were the incidence of recurrent IS and total stroke events (defined as the combined occurrence of ischemic and hemorrhagic strokes). IS was defined as an acute focal infarction of the brain or retina, characterized by the sudden onset of a new focal neurological deficit with clinical or imaging evidence of infarction that was not attributable to non-ischemic causes, such as brain infection, trauma, tumor, seizure, severe metabolic disease, or neurodegenerative disorders. Hemorrhagic stroke was defined as acute extravasation of blood into the brain parenchyma or subarachnoid space, accompanied by associated neurological symptoms and confirmed by imaging evidence.

Secondary outcomes included functional outcomes assessed using the m-*RS* and Barthel index at the end of the study and all-cause mortality. The functional outcomes were assessed to determine the degree of disability and independence in daily activities, while mortality data were collected from hospital records or death certificates. Functional recovery was classified as poor if the m-*RS* score was ≥3, and the m-*RS* scores at follow-up were compared between the NBP and control groups. Barthel index ≤60 was considered to be dependent on activities of daily living for stroke prognosis, and > 60 was considered to have a good outcome.[21]

Statistical Analysis

Descriptive statistics were calculated for both continuous and categorical variables. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of the data. Categorical variables were presented as frequencies and percentages. The normality of continuous data was assessed using the Shapiro–Wilk test. Differences between the NBP and control groups for continuous variables were assessed using the independent samples *t*-test for normally distributed data, and the Mann–Whitney *U*-test was employed for non-normally distributed data. Categorical variables were compared between groups using the chi-square test or Fisher's exact test when the expected frequencies were low.

To test our hypothesis that NBP treatment reduces stroke recurrence, especially in male and younger patients, we used multivariate logistic regression models to adjust for potential confounding factors. The selection of covariates for the multivariate analysis was guided by both clinical relevance and statistical significance observed in the univariate analysis ($P < 0.10$). The following factors were included in the multivariate analysis: age, gender, BMI, smoking status, alcohol consumption, history of hypertension, diabetes, hyperlipidemia, coronary artery disease, and baseline m-*RS* score. Any other variables that showed significant differences between the two groups at baseline were also included as covariates. The relative risk (RR) and 95% confidence intervals (CI) were calculated to estimate the association between NBP use and study outcomes. To assess the potential effects of age and sex, univariate and multifactorial analyses were performed in subgroups, with Bonferroni correction used for univariate analysis and significance defined as a bilateral P value <

0.01. A two-sided P-value of <0.05 was used to define statistical significance. All statistical analyses were conducted using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Between April 16, 2021, and March 16, 2022, a total of 1,190 patients with IS were recruited for the study. Of these, 596 patients were assigned to the NBP group, and 594 patients were assigned to the control group. Over the 12-month follow-up period, 81 participants were either lost to follow-up or withdrew from the study. Consequently, data from 1,109 patients (538 in the NBP group and 571 in the control group) were included in the final analysis (Figure 1).

Baseline Characteristics

The final cohort consisted of 1,109 IS patients, with 538 in the NBP group and 571 in the control group. Among the participants, 345 (64.1%) of the NBP group were male, while 402 (70.4%) of the control group were male. Conversely, the proportion of female participants was higher in the NBP group (35.9%) than in the control group (29.6%), and this difference in gender distribution was statistically significant (P = 0.026) (Table 1).

Primary Outcome Events, Functional Outcomes, and Mortality

After 12 months of follow-up, the incidence of recurrent IS was significantly lower in the NBP group (7.4%, 40/538) compared to the control group (10.9%, 62/571) (P = 0.049). Similarly, the total incidence of stroke events, which included both ischemic and hemorrhagic strokes, was significantly reduced in the NBP group (7.8%, 42/538) compared to the control group (11.6%, 66/571) (P = 0.035).

In terms of functional outcomes, there were no significant differences in m-*RS* group between the NBP and control groups at 12 months. The proportion of patients with m-*RS* scores of ≥3 was 10.8% in the NBP group and 10.3% in the control group (P = 0.808), indicating that the addition of NBP did not significantly influence functional recovery. There was also no significant difference in Barthel index scores (P=0.192), and the proportion of patients with Barthel index > 60 was 93.5% in the NBP group and 91.4% in the control group. Mortality rates were also similar between the two groups, with 0.9% (5/538) of patients in the NBP group and 1.6% (9/571) of patients in the control group dying during the study period (P = 0.335) (Table 2).

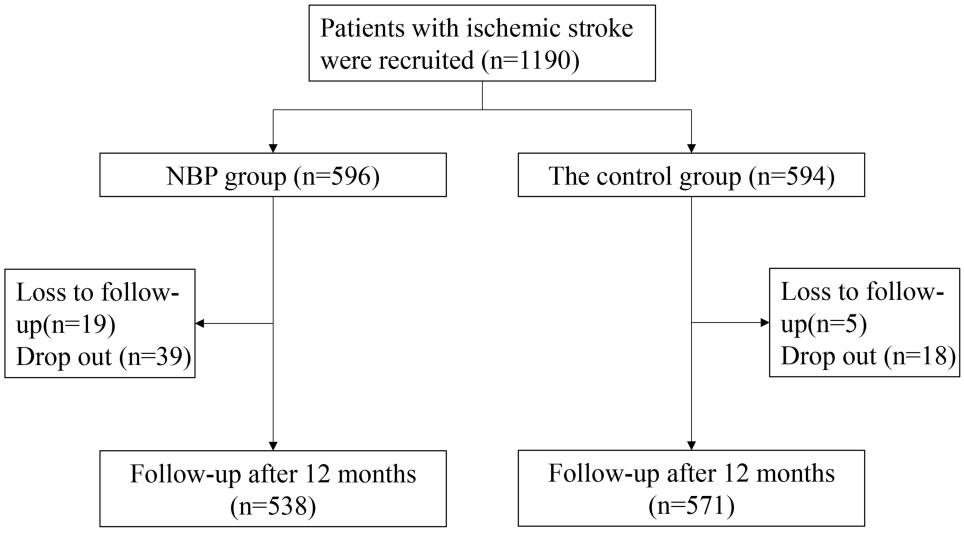

Figure 1 Flowchart of the study. Figure showed that the study design and follow-up of patients with ischemic stroke. Initially, 1190 patients were recruited and divided into the NBP group (596) and the control group (594). During the 12-month follow-up, 19 patients in the NBP group were lost to follow-up, and 39 patients dropped out, resulting in 538 patients completing the follow-up. In the control group, 5 patients were lost to follow-up, and 18 patients dropped out, resulting in 571 patients completing the follow-up.

Table 1 Baseline Data of NBP Group and Control Group

Features	NBP Group (n=538)	Control Group (n=571)	P
Gender, n (%):			
Male	345 (64.1)	402 (70.4)	0.026
Female	193 (35.9)	169 (29.6)	
Age group, n (%)	62.31 (8.67)	62.75 (8.30)	0.388
<60 years	194 (36.1)	196 (34.3)	0.833
60 years ~	219 (40.7)	239 (41.9)	
≥70 years,	125 (23.2)	136 (23.8)	
BMI group, n (%)	26.67 (3.86)	26.43 (3.24)	0.259
<24 Kg/m^2	119 (22.1)	126 (22.1)	0.480
24 Kg/m^2 ~	242 (45.0)	275 (48.2)	
≥28 Kg/m^2	177 (32.9)	170 (29.8)	
Waist-hip ratio, means (SD)	0.96 (0.44)	0.93 (0.07)	0.099
Smoking, n (%):			
Never	254 (47.2)	209 (36.6)	<0.001
Smoking cessation	189 (35.1)	211 (37.0)	
Smoke	95 (17.7)	151 (26.4)	
Alcohol consumption, n (%):			
Never	276 (51.3)	263 (46.1)	<0.001
Stop drinking	208 (38.7)	203 (35.6)	
Drinking	54 (10.0)	105 (18.4)	
Hypertension, n (%)			
Yes	421 (78.3)	415 (72.7)	0.031
No	117 (21.7)	156 (27.3)	
Diabetes, n (%)			
Yes	184 (34.2)	172 (30.1)	0.146
No	354 (65.8)	399 (69.9)	
Hyperlipidemia, n (%)			
Yes	253 (47.0)	224 (39.2)	0.009
No	285 (53.0)	347 (60.8)	
Coronary heart disease, n (%)			
Yes	74 (13.8)	72 (12.6)	0.573
No	464 (86.2)	499 (87.4)	
Glycated hemoglobin, %, means (SD)	6.35 (1.28)	6.39 (1.36)	0.595
Homocysteine, μmol/l, means (SD)	17.16 (11.90)	18.46 (15.27)	0.113
Triglycerides, mmol/l, means (SD)	1.62 (1.11)	1.61 (1.14)	0.892
Total cholesterol, mmol/l, means (SD)	4.38 (1.05)	4.43 (1.10)	0.412
HDL, mmol/l, means (SD)	1.21 (0.28)	1.22 (0.28)	0.437
LDL, mmol/l, means (SD)	2.52 (0.87)	2.56 (0.90)	0.468
hs-CRP, mg/l, median (IQR)	1.42 (2.30)	1.55 (2.51)	0.004
Baseline m-*RS* group, n (%)			
m-RS<3	453 (84.25)	501 (87.7)	0.089
m-RS≥3	85(15.8)	70 (12.3)	
Baseline Barthel index, median (IQR)	100(0)	100(0)	0.122
Barthel index≤60, n (%)	41(7.6)	37(6.5)	0.458
Barthel index>60, n (%)	497(92.4)	534(93.5)	

Abbreviations: NBP, N-butylphthalide; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Univariate Analysis of Prognostic Factors

Univariate logistic regression analysis identified several factors associated with the occurrence of IS during the 12-month follow-up period. These factors included NBP treatment, BMI category, hypertension, triglycerides, hs-CRP, and

Table 2 Outcome Events in NBP Group and Control Group During the 12-month Study Period (Number of People)

Features	NBP Group (n=538)	Control Group (n=571)	P
Ischemic stroke, n (%)	40 (7.4)	62 (10.9)	0.049
Hemorrhagic stroke, n (%)	3 (0.6)	5 (0.9)	0.727
Stroke, n (%)	42 (7.8)	66 (11.6)	0.035
m-*RS group* after 12 months, n(%)			
m-RS<3	480 (89.2)	512 (89.7)	0.808
m-RS≥3	58 (10.8)	59 (10.3)	
Barthel index	100(0)	100(0)	0.277
Barthel index≤60, n (%)	35(6.5)	49(8.6)	0.192
Barthel index>60, n (%)	503(93.5)	522(91.4)	
Death, n (%)	5 (0.9)	9 (1.6)	0.335

baseline m-*RS* score. Among these, NBP treatment, hypertension, triglycerides, hs-CRP, and baseline m-*RS* score were associated with stroke recurrence (P < 0.1) (Tables S1 and S2).

Multivariate Analysis of Prognostic Factors

To assess the independent effect of NBP on stroke outcomes, a multivariate logistic regression analysis was conducted. The analysis adjusted for potential confounding factors, including age, gender, BMI, smoking status, alcohol consumption, history of hypertension, diabetes, hyperlipidemia, coronary artery disease, and baseline m-*RS* score.

The results confirmed that NBP treatment was independently associated with a reduced risk of recurrent IS (RR = 0.610, 95% CI: 0.399–0.931, P = 0.022). Additionally, NBP treatment reduced the risk of total stroke events (RR = 0.604, 95% CI: 0.400–0.912, P = 0.016) (Tables S1 and S2).

Subgroup Analysis

In univariate analysis, patients aged 60–70 years showed significantly reduced recurrence rates of both ischemic (P = 0.010) and total stroke (P = 0.007) in the NBP group after Bonferroni correction. Other subgroups did not reach statistical significance under the corrected threshold of P < 0.01 (Table 3).

Table 3 Subgroup Analysis of Primary Outcome Events

Features	NBP Group (n=538)	Control Group (n=571)	P
Ischemic stroke, n (%)	40 (7.4)	62 (10.9)	0.049
Gender, n (%):			
Male	21/345 (6.1)	42/402 (10.4)	0.032
Female	19/193 (9.8)	20/169 (11.8)	0.542
Age Group, n (%):			
<60	11/194 (5.7)	23/196 (11.7)	0.034
60~	11/219 (5.0)	28/239 (11.7)	0.010
≥70	18/125 (14.4)	11/136 (8.1)	0.105
Stroke, n (%)	42 (7.8)	66 (11.6)	0.035
Gender, n (%):			
Male	22/345 (6.4)	44/402 (10.9)	0.028
Female	20/193 (10.4)	22/169 (13.0)	0.431
Age Group, n (%):			
<60	11/194 (5.7)	24/196 (12.2)	0.023
60~	11/219 (5.0)	29/239 (12.1)	0.007
≥70	20/125 (16.0)	13/136 (9.6)	0.118

Notes: Bonferroni correction applied for multiple comparisons; adjusted statistical significance threshold set at P < 0.01.

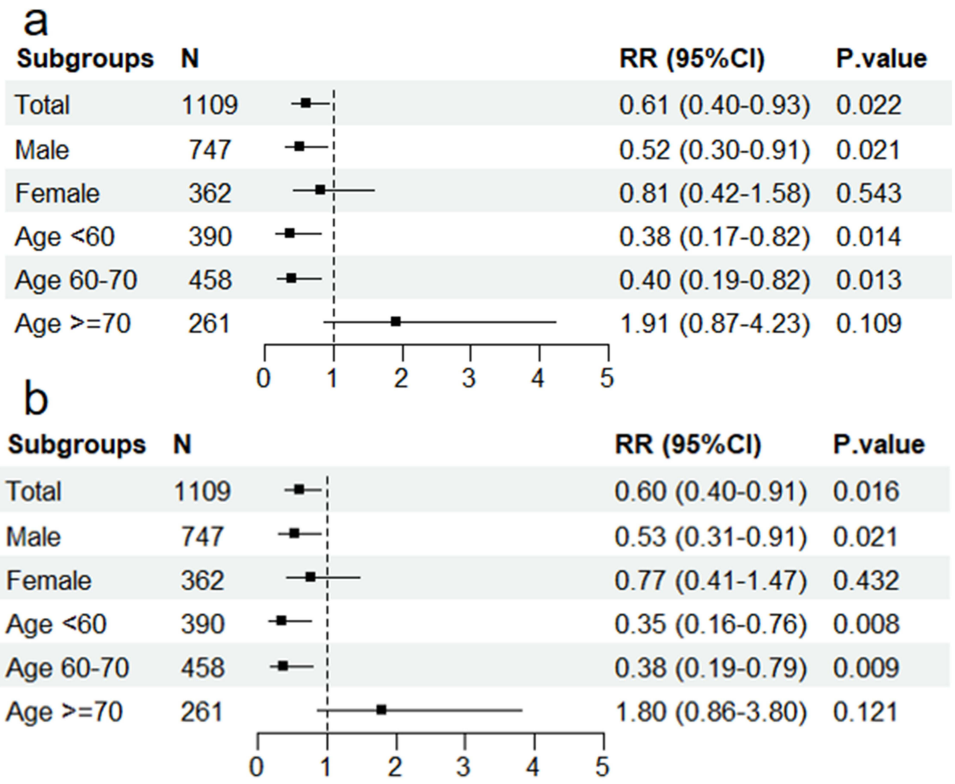

Figure 2 Multivariate logistic regression results of subgroup analysis in the primary outcomes. Figure showed the multivariate logistic regression results of NBP on ischemic stroke recurrence (**a**) and stroke occurrence (**b**) within 12 months of the study individuals. The figure listed the sample size (N), relative risk (RR), 95% confidence interval (CI), and P-value for different genders and age groups. 2a showed multivariate logistic regression results of ischemic stroke recurrence. The total sample size was 1109, with males 747 and females 362. The relative risk for the male group was 0.521 (95% CI:0.299–0.907), P=0.021; for the age <60 group was 0.377 (95% CI: 0.173–0.822), P=0.014; and for the age 60–70 group was 0.399 (95% CI: 0.193–0.821), P=0.013. 2b showed multivariate logistic regression results of stroke occurrence. The total sample size was 1109, with males 747 and females 362. The relative risk for the male group was 0.528 (95% CI:0.307–0.907), P=0.021; for the age <60 group is 0.352 (95% CI: 0.163–0.758), P=0.008; and for the age 60–70 group was 0.383 (95% CI: 0.186–0.787), P=0.009.

In multivariate logistic regression (Figure 2), NBP use was independently associated with reduced stroke recurrence in male patients (RR = 0.521; 95% CI: 0.299–0.907; P = 0.021) and in those under 70 years. These subgroup effects were exploratory and not adjusted for multiple comparisons, and thus should be interpreted cautiously.

In addition, we further explored the effect of NBP on mortality in both the recurrent and non- recurrent subgroups, and the outcome was not significant (P > 0.05) (Table S3).

Discussion

This study aimed to evaluate the efficacy of NBP in reducing stroke recurrence over a 12-month period in patients with a history of IS. The findings demonstrated that NBP significantly decreased the incidence of recurrent IS by 39% compared to the control group. One of the most notable observations was the gender-specific effect of NBP: the reduction in stroke recurrence was more pronounced in male patients, while the effect in female patients did not reach statistical significance. The analysis also revealed an age-dependent efficacy of NBP. The protective effects were most pronounced in patients under 70 years of age. In contrast, patients aged 70 years and older did not exhibit a significant reduction in stroke recurrence. Additionally, NBP reduced the overall incidence of stroke, including both ischemic and hemorrhagic strokes, by 39.6%. Despite these significant reductions in stroke recurrence, no notable differences were observed between the NBP and control groups in terms of functional outcomes, as measured by the m-RS, or in all-cause mortality.

Relatively little research has been done on stroke recurrence, and previous studies have focused on the short-term benefits of NBP, particularly its role in reducing mortality and improving functional outcomes in the acute phase of IS. When administered during this phase, NBP significantly reduces neurological deficits and enhances functional recovery without increasing the risk of adverse events.[11,12] While a few studies have suggested potential benefits, these were often

limited by small sample sizes and short follow-up periods, making it difficult to draw definitive conclusions.[22] A prospective multi-center short-term follow-up study concluded that the risk of relapse of IS was lower in the NBP non-compliance group than in the stroke non-recurrence group.[23] In contrast to previous findings, this study demonstrated that NBP significantly reduced the incidence of recurrent IS by 39% compared to the control group. The study's large sample size and robust statistical analysis lend strong support to the conclusion that NBP offers substantial protective effects against stroke recurrence. Unlike earlier studies, which focused on the short-term impact of NBP during the acute phase, the present study highlights the potential long-term benefits of NBP when used beyond the acute stage. Although our study found that NBP reduced recurrence rates, it did not significantly reduce mortality, even in the relapsed and non-relapsed subgroups. This may be due to the fact that we selected stroke patients who were in the recovery period more than 1 month before the study but less than 6 months, and these patients have passed the critical period, and the mortality will be significantly reduced. At the same time, the small number of deaths in our two groups and the short follow-up time may not reflect the outcome well, so the reliability of the test needs to be verified. In the future, the follow-up time will be further increased to verify the impact of NBP on stroke mortality. The observed reduction in stroke recurrence may be explained by several mechanisms of NBP. NBP is known to preserve mitochondrial function and enhance energy metabolism, which helps stabilize the neuronal environment and may prevent recurrent ischemic events.[8,9] Additionally, NBP exhibits anti-inflammatory and antioxidative properties, which could reduce the overall burden of cerebrovascular risk factors, thereby lowering the likelihood of subsequent strokes.[10]

While several studies have evaluated the neuroprotective properties of NBP, its impact on the overall incidence of both ischemic and hemorrhagic strokes has not been extensively documented. Most prior research has focused on isolated outcomes, such as the recurrence of IS, without considering the broader spectrum of stroke risks. One study reported that NBP, when administered during the acute phase of IS, not only reduced the severity of neurological deficits but also appeared to offer a protective effect against subsequent strokes. However, this study primarily focused on short-term outcomes and did not evaluate the long-term vascular benefits of NBP.[12] Another i study suggested that NBP might reduce the risk of myocardial infarction when used as part of a comprehensive treatment regimen, but it did not specifically quantify the reduction in the total incidence of stroke.[11] Similarly, a meta-analysis of randomized controlled trials on NBP emphasized its safety and efficacy in reducing neurological damage in IS patients. While the analysis confirmed that NBP reduces mortality and disability, it did not specifically address its impact on the combined risk of ischemic and hemorrhagic strokes.[12] In the current study demonstrated that NBP significantly reduced the total incidence of IS and overall stroke events (including both ischemic and hemorrhagic strokes) by 39.6% and 36.4%, respectively. These findings suggest that NBP could be a vital component of stroke risk management, particularly in patients with a history of IS. The broad-spectrum protective effects of NBP observed in this study may be attributed to several mechanisms. NBP is known to improve mitochondrial function, enhance energy metabolism, and reduce oxidative stress, all of which likely play a key role in stabilizing vascular integrity and preventing the onset of both ischemic and hemorrhagic strokes.[8,10] Furthermore, NBP's anti-inflammatory properties may contribute to its ability to mitigate stroke risk, as chronic inflammation and endothelial dysfunction are well-known triggers of stroke.[9,24,25] Another possible mechanism is NBP's influence on lipid metabolism and its potential anti-atherosclerotic effects, which help maintain vascular health and reduce the likelihood of future strokes.[26]

Previous research on gender differences in stroke outcomes has revealed that female patients generally experience worse functional outcomes and higher mortality rates after stroke compared to males, although these studies did not specifically evaluate the impact of NBP on stroke recurrence.[14] Studies on thrombolysis and endovascular treatment for acute IS have shown that both male and female patients benefit from these therapies. However, females often experience poorer outcomes, potentially due to older age at stroke onset and the presence of comorbidities.[27] Another study highlighted differences in platelet reactivity and the response to antiplatelet therapy between males and females, suggesting that gender may influence the efficacy of certain stroke treatments.[28] However, this study did not explore the impact of NBP or its long-term effects on stroke recurrence. Similarly, an analysis of 279 patients who received endovascular therapy found that males and females responded differently to the treatment, but NBP was not specifically addressed.[29] The current study's finding that NBP significantly reduced stroke recurrence in male patients, but not in female patients, is novel and suggests a potential gender-specific response to NBP treatment. Several mechanisms may

explain the observed gender differences in NBP efficacy. Biological differences, such as hormonal influences, could play a role in how males and females metabolize and respond to NBP. For instance, estrogen has been shown to exert both neuroprotective and neurotoxic effects, depending on the context, and it may interact with the pathways through which NBP exerts its effects.[15] Additionally, gender-based differences in platelet function could influence the effectiveness of NBP in preventing stroke recurrence.[28] Studies have shown that female stroke patients have higher platelet counts but lower platelet response to agonists, which may affect the effectiveness of antithrombotic therapy.[30] In addition, in female patients with acute stroke, the neutrophil count is increased, and the inflammatory response is active in the body, which may also cause the effect of NBP treatment to be weakened.[30] The higher baseline incidence of recurrent strokes in males may make the protective effects of NBP more detectable in this group, while the relatively lower baseline risk in females could contribute to the absence of statistically significant findings in this subgroup. This gender difference in NBP efficacy has not been widely reported in prior studies, suggesting that gender may be an important factor influencing NBP's therapeutic effects. These differences could be attributed to biological or pharmacokinetic factors that warrant further investigation to optimize stroke prevention strategies in male and female patients.

The influence of age on the efficacy of NBP in reducing stroke recurrence has not been widely explored. Most prior studies on NBP have focused on its overall efficacy in stroke management, without explicitly investigating how age might alter its therapeutic effects. Research on stroke recurrence has consistently shown that older patients are at a higher risk of recurrent stroke and tend to have poorer outcomes compared to younger patients. However, these studies rarely assess the differential impact of specific treatments, such as NBP, across different age groups.[16] Evidence from studies on antiplatelet therapy in stroke prevention indicates that younger patients generally respond better to treatment, with lower recurrence rates compared to older patients. This difference is attributed to age-related physiological changes, such as reduced drug metabolism and altered vascular responsiveness. However, these studies did not specifically investigate the effects of NBP.[31] Additionally, research on neuroprotective agents in general suggests that their efficacy declines with age, possibly due to factors such as reduced drug metabolism, a higher prevalence of comorbidities, and a decline in physiological resilience. While this trend has been noted with other neuroprotective agents, it has not been explicitly studied in the context of NBP.[32] The present study provides clear evidence that the protective effects of NBP against stroke recurrence are most pronounced in patients under 70 years of age, with the greatest benefit observed in those younger than 60 years. In contrast, patients aged 70 years and older did not experience a significant reduction in stroke recurrence. This finding is particularly noteworthy as it highlights the age-dependent efficacy of NBP, suggesting that younger patients derive greater benefit from NBP therapy in the context of secondary stroke prevention. These results emphasize the importance of tailoring treatment strategies based on patient age, especially when considering the long-term use of NBP for stroke prevention. Several mechanisms may explain the observed age-related differences in the efficacy of NBP. Younger patients may have a more robust physiological response to NBP, which includes better drug absorption, more efficient metabolism, and greater cellular resilience. In contrast, age-related changes in hepatic and renal function may reduce the bioavailability and efficacy of NBP in older patients. Older adults also tend to have a higher burden of comorbidities, which may interfere with the therapeutic effects of NBP and reduce its effectiveness in preventing stroke recurrence.[16] With age, neuroplasticity declines, which can affect the brain's ability to adapt and recover from injury.[33] In addition, with age, blood vessels become less elastic and stiffer, which is associated with an increased risk of cardiovascular events, including stroke.[34] The Systemic Inflammatory Response Index (SIRI) is associated with all-cause mortality in stroke patients, while aging and declining immune system function lead to chronic low-grade inflammation that increases the risk of stroke.[35,36] To sum up, these factors likely contribute to the diminished efficacy of NBP in patients aged 70 years and older. These findings underscore the need for age-specific treatment strategies in stroke prevention. While younger patients may achieve significant benefits from NBP, older patients may require alternative or adjunctive therapies to achieve comparable protective effects. This age-dependent response highlights the importance of personalized medicine in stroke prevention, particularly in the context of secondary prevention strategies.

The potential of NBP to improve neurological function in stroke patients has been the focus of several studies, particularly in the context of acute stroke management. It is well-documented that NBP can reduce neurological deficits and enhance short-term functional outcomes. However, its long-term impact on functional recovery and survival,

especially beyond the acute phase, remains less conclusive. A randomized controlled trial demonstrated that NBP significantly improved m-*RS* scores at 90 days in patients who received NBP treatment during the acute phase of IS.[11] Another study focusing on the short-term effects of NBP found that patients treated with NBP had better outcomes on the Barthel Index, which measures performance in activities of daily living.[12] Research involving patients with large vessel occlusion stroke further demonstrated that NBP, when combined with endovascular therapy, improved functional outcomes at 90 days without increasing the risk of adverse events.[13] Similarly, a systematic review and meta-analysis of NBP's effects on IS concluded that while NBP is effective in reducing mortality and dependency during the acute phase, its long-term impact on functional outcomes remains unclear.[12] The current study revealed that NBP did not result in a significant improvement in functional outcomes, as measured by the m-*RS* and Barthel index, nor in all-cause mortality. This suggests that while NBP may be effective in preventing new vascular events, its influence on long-term functional recovery and survival may be limited. NBP did not significantly improve long-term neurological function, which may be due to the complexity and diversity of factors affecting stroke recovery.[8–10]

This study has several limitations. First, while the sample size was relatively large, it was conducted in Jizhou District, Tianjin, which may limit the generalizability of findings to other populations with different demographic or clinical characteristics, and more multicentre trials in different populations are needed to confirm these results. As for the NBP group and the control group, the recruitment season was in spring, summer and summer and autumn respectively, and the winter was staggered, which reduced the season with the worst prognosis of stroke, and minimized the confusion of stroke caused by differences in recruitment seasons.[37,38] Second, the 12-month follow-up period captured only the short-term benefits of NBP and did not evaluate its long-term effects on stroke recurrence, functional outcomes, or survival. Extending the follow-up period in future studies would provide a clearer understanding of NBP's sustained efficacy and safety. Third, the study assessed functional outcomes using only the m-*RS* and BI indices, assessing daily living ability as much as possible for disease prognosis. But the study focused specifically on recovering individuals whose strokes occurred more than one month before the study but less than six months, all of whom were community residents. Therefore, acute clinical data, including the national institutes of health stroke scale (NIHSS) scores, may not be necessary for this particular study population. Data such as infarct volume, which we did not collect, will be more widely included in future studies and the results will be multi-validated. Fourth, despite adjustments for several confounders, residual confounding from unmeasured factors, such as stroke severity and rehabilitation intensity cannot be ruled out. Fifth, the study used staged cluster sampling rather than full randomization. While this approach allowed for actual recruitment in a community-based environment, it can introduce selection bias. The inclusion of more comprehensive covariates and the use of advanced statistical methods, such as propensity score matching (PSM), can reduce bias while balancing out differences in medication use for baseline standard care. However, this method was not used in our study due to the limitation of sample size, and the use of PSM will greatly reduce our sample size. However, to minimize the impact of potential confounders, we included a number of covariates in our analysis, adjusting for baseline differences between groups as much as possible. Sixth, we used logistic regression rather than Cox regression because there is a fixed time point to understand the effect of NBP on one-year prognosis after stroke, and future studies will analyze the effect over time. We adjusted multiple potential confounders in the model, pre-processed the data, identified and processed potential outliers, and ensured sufficient sample size to improve the stability and accuracy of the model, which was applicable in this study. Lastly, although the study identified significant differences in NBP efficacy by gender and age, these subgroup analyses were not the primary focus and may lack sufficient statistical power. Future studies should be designed to specifically evaluate these subgroup differences, using stratified analyses to provide more robust insights into potential effect modifiers.

Conclusion

This study demonstrates that NBP significantly reduces IS recurrence and total stroke events over 12 months, with particularly notable benefits in male patients and those under 70 years of age. These findings highlight the potential of NBP as an effective strategy for secondary stroke prevention and address the urgent need to reduce recurrence rates and the associated healthcare burden by more targeted treatment of a specific population (< 70 years, men). While NBP did not improve long-term functional outcomes or survival, its preventive effects against recurrent vascular events underscore its

clinical value. Future studies should explore the long-term (2 years and above) efficacy of NBP in broader populations and assess its integration into personalized treatment strategies to optimize secondary prevention in IS survivors.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest. The study was independently conducted by the academic investigators without any influence from the sponsor.

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