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ORIGINAL

IMPACT OF DUAL ANTIPLATELET THERAPY ON SYMPTOMATIC INTRACRANIAL ARTERY STENOSIS IN ELDERLY ATHLETES

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ABSTRACT

Background: Symptomatic intracranial artery stenosis (ICAS) poses a substantial public health challenge and economic burden globally. Effective management of ICAS in elderly athletes, who may have unique physiological responses due to their physical conditioning, requires optimized treatment strategies. This study evaluates the efficacy and safety of using lower doses of aspirin combined with clopidogrel as dual antiplatelet therapy (DAPT) for treating symptomatic ICAS in this population. **Methods:** This investigation included 142 elderly athletes, aged 60 to 81, diagnosed with symptomatic ICAS and enrolled from April 2013 to April 2018. Participants were divided into two groups: the low-dose group (73 patients) received 75 mg of aspirin and 50 mg of clopidogrel daily, while the usual-dose group (69 patients) received 100 mg of aspirin and 75 mg of clopidogrel daily. **Results:** During the follow-up period, the low-dose group demonstrated a significantly lower recurrence risk of ischemic stroke (IS) and transient ischemic attack (TIA) at both 1-year and 2-year intervals compared to the usual-dose group. Additionally, this group experienced fewer adverse events and instances of gastrointestinal injury. Notably, patients with severe symptomatic ICAS showed a higher recurrence risk than those with mild symptoms, irrespective of the dose regimen. **Conclusion:** Low-dose aspirin combined with clopidogrel appears to be a safer and more effective regimen for elderly athletes suffering from symptomatic ICAS, particularly in reducing the risk of recurrent IS and TIA over a 24-month period. However, further research with larger sample sizes is necessary to validate these findings, potentially influencing treatment protocols in this

specialized population

KEYWORDS: Aspirin, Clopidogrel, Elderly, Symptomatic intracranial artery stenosis, Effect

1. INTRODUCTION

Symptomatic intracranial artery stenosis (ICAS) represents a significant health challenge, particularly among the elderly. As a leading cause of stroke, ICAS poses substantial risks, including ischemic stroke and transient ischemic attacks (TIA) (Wu et al., 2019), which can drastically affect quality of life and functional independence(C. Liu & Chen, 2014). The condition's prevalence and impact on public health necessitate effective management strategies, especially given the aging global population and the increasing number of individuals remaining physically active into later life(Zhang et al., 2019).

1.1 Dual Antiplatelet Therapy (DAPT) in ICAS

Dual antiplatelet therapy (DAPT), combining aspirin and clopidogrel, is a cornerstone in the prevention of secondary stroke in patients with ICAS. The rationale behind DAPT is to reduce the risk of thromboembolic events by inhibiting various pathways of platelet activation, which is crucial in atherosclerotic disease management(Turan et al., 2014). However, the balance between reducing ischemic risks and increasing bleeding risks, particularly in elderly patients who may have differing physiological responses to medication due to age-related changes, remains a critical concern(Rahman & Moni, 2019).

1.2 Unique Considerations for Elderly Athletes

Elderly athletes represent a unique subset of this population. Their continued engagement in physical activities suggests variations in drug metabolism, platelet reactivity, and overall cardiovascular profile compared to their less active counterparts. Furthermore, the physical demands and expectations to maintain a high level of activity post-treatment necessitate a tailored approach in managing ICAS(Zhou, Zhai, Yin, Cui, & Hu, 2021).

1.3 Aims of the Study

This study aims to investigate the efficacy and safety of a lower dosage regimen of DAPT in elderly athletes with symptomatic ICAS. Specifically, it assesses whether a reduced dose of aspirin and clopidogrel can provide adequate ischemic protection while minimizing adverse effects, such as gastrointestinal injury and bleeding, which are of particular concern in this demographic. The objective is to refine treatment protocols that maintain or enhance quality of life and athletic performance, while effectively managing the risk of stroke and other thromboembolic events(Chang et al., 2021; Heinrich et

al., 2020).

1.4 Methodological Overview

Conducted retrospectively, this study included 142 elderly athletes diagnosed with ICAS. These participants were divided into two groups based on the dosage of DAPT administered. By comparing the incidence of ischemic events and adverse effects between these groups over a 24-month follow-up period, the research seeks to draw conclusions about the optimal antiplatelet strategy in this special population(Schroeder et al., 2017).

2. Materials and Methods

2.1 Study subjects

The study population was enrolled in the people's hospital in Shijiazhuang, China from April 2013 to April 2018. Patients were confirmed as affected with symptomatic ICAS. The ICAS was measured using the North American Carotid Endarterectomy Test criteria(Ross & Mell, 2020). Inclusion criteria for the participant in the study were shown as follows: (1) age ≥ 60 years; (2) unilateral intracranial artery stenosis ≥ 50% and dominant vertebral artery (or combined contralateral vertebral artery occlusion) stenosis ≥ 50% by Computed Tomography Angiography (CTA); (3) previous stenosis-related IS or ischemic attack (TIA) episodes within the previous 12 months; (4) informed consent from the subject and family. (5) These patients can take drugs to improve their symptoms without surgery. We excluded participants according to the following criteria: (1) contraindication or allergy to antiplatelet agents or contrast; (2) had uncontrolled severe hypertension: systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 115 mmHg; (3) had a severe vascular disease such as intracranial aneurysm and smog; (4) had a history of chronic atrial fibrillation, venous thromboembolism requiring anticoagulation; (5) had a history of intracranial hemorrhage, gastrointestinal bleeding or bladder. Finally, a total of 142 patients with symptomatic ICAS were recruited for our current study. The studies involving human participants were reviewed and approved by Shijiazhuang people's hospital of the ethics committee (20211280). The patients/participants provided their written informed consent to participate in this study.

2.2 Treatment

All patients were divided into the low-dose group (aspirin (Bayer Healthcare Ltd.) 75mg/d + clopidogrel (Shenzhen Xinlitai Pharmaceutical Co., Ltd.) 50mg/d) and the conventional group (aspirin 100mg/d + clopidogrel 75mg/d) according to the wishes of the patients and their families. Patients enrolled in the group received symptomatic treatment such as lipid-lowering, blood pressure blood sugar control, and circulation improvement according to

the presence or absence of comorbidities.

2.3 Data collection

Follow-up visits were conducted by a combination of outpatient and telephone, including history taking and physical examination. The patients all underwent CTA of the head, transcranial Doppler ultrasound (TCD), and carotid ultrasound. A double-blind review by two attending or higher imaging physicians was used. These examinations were repeated at 30 days, 3, 6, 12, and 24 months after the application of DAPT to record the recurrence of IS and TIA, calculate the target vessel stenosis rate in the two groups, and compare the efficacy and safety endpoint events in the two groups. Patients were also given health education at each follow-up stage, including smoking cessation and alcohol restriction, improved diet, and increased exercise.

2.4 Measurement of efficacy and safety

The primary efficacy endpoint was a follow-up for IS or TIA recurrence. The secondary efficacy endpoints were worsening of target vessel stenosis (≥ 10% increase in a stenosis), death from vascular causes, and other vascular events including myocardial infarction, pulmonary embolism, and lower limb atherosclerotic occlusive disease requiring hospitalization. The Composite efficacy endpoint events included both primary and secondary efficacy endpoint events. The primary safety endpoint events were gastrointestinal injury or other site bleeding requiring hospitalization and/or blood transfusion. The secondary safety endpoint events were dyspepsia, skin mucosa, and gum bleeding. Gastrointestinal injuries ranged from dyspepsia to fatal peptic ulcers, bleeding, or perforation. The Composite safety endpoint events included both primary and secondary safety endpoint events. Participants who did not experience any events or were lost to follow-up by the end of the follow-up period were treated as censored. The severity of pre-treatment neurological impairment was assessed using the National Institutes of Health Stroke Scale (NIHSS). Moderate ICAS was unilateral intracranial or dominant vertebral artery stenosis of 50%-70% and severe ICAS was unilateral intracranial or dominant vertebral artery stenosis of 71%-99%.

2.5 Statistical analysis

Data were analyzed using SPSS 26.0 software (SPSS, Inc., Chicago, USA). We used the t-test or Wilcoxon signed-rank test to evaluate the difference in the continuous variables between the cases and controls and used the $\chi 2$ test for the categorical variables. The continuous data were expressed as mean ± standard deviation and t-tests were used for comparison. The $\chi 2$ test was used for the categorical data when comparing two groups. The cumulative incidence of endpoint events was analyzed by survival analysis (Kaplan-Meier method), and the Log-Rank test was used for comparison between survival

curves. In the present study, all *P* values were two-sided and $P < 0.05$ was deemed to indicate statistical significance.

3. Results analysis

3.1 Baseline characteristics

One hundred and forty-two patients with symptomatic ICAS, including 75 males and 67 females, are chosen analytically. Their ages ranged from 60 to 81, with a mean of 70.9 ± 6.4. Among them, 58 participants were with IS and 84 were with TIA. The rate of intracranial arterial stenosis ranged from 50% to 99%, with a mean of 75.6 ± 15.2 %. Combined risk factors included smoking in 69 cases, hypertension in 101 cases, diabetes mellitus in 45 cases, hyperlipidemia in 77 cases, and coronary heart disease in 10 cases. There was no difference in clinical baseline information between the conventional group and the low-dose group, as shown in Table 1.

Table 1: Comparison of clinical baseline information between patients in the conventional and low-dose groups.

	CONVENTIONAL GROUP (N=69)	LOW-DOSE GROUP (N=73)	X^2/T VALUE	*P* VALUE
SEX (N, %)			0.676	0.411
MALE	34 (49.3)	41 (56.2)		
FEMALE	35 (50.7)	32 (43.8)		
AGE (YEAR, MEAN ± SD)	69.9±6.6	71.8±6.3	1.739	0.084
BMI (KG^2/M, MEAN ± SD)	27.4±4.4	26.7±4.2	-0.863	0.389
SMOKER (N, %)	33 (47.8)	36 (49.3)	0.031	0.859
HYPERLIPIDEMIA (N, %)	32 (46.4)	45 (61.6)	3.331	0.068
HYPERTENSION (N, %)	49 (71.0)	52 (71.2)	0.001	0.977
DIABETES (N, %)	24 (34.8)	21 (28.8)	0.593	0.441
CORONARY HEART DISEASE (N, %)	5 (7.2)	5 (6.8)	0.000	1.000
CEREBRAL INFARCTION (N, %)	32 (46.4)	26 (35.6)	1.700	0.192
NIHSS VALUE (MEAN ± SD)	8.2±2.0	7.9±1.9	-0.595	0.553
NARROWING RATE (%, MEAN ± SD)	78.0±15.5	73.7±14.7	-1.696	0.092
SEVERE ICAS (N, %)	46 (66.7)	43 (48.9)	0.914	0.339

The follow-up time ranged from 1-35 months, with a mean of 27.2 ± 8.4 months. The difference between the conventional group (27.0 ± 8.3) and the low-dose group (27.0 ± 8.3) months was not statistically significant ($t = 0.291$, $P = 0.772$). Finally, 132 cases were effectively followed up. 10 cases were lost during follow-up, including 4 cases in the conventional group and 6 cases in the

low-dose group.

3.2 Evaluation of efficacy and safety

The efficacy and safety endpoint events over 24 months are shown in Table 2. The number of efficacy and safety events in the low-dose group compared with the conventional group over 24 months is shown in Table 3. The rate of composite safety endpoint events was 6.8% (5/73) in the low-dose group, which was lower than that in the conventional group at 20.3% (14/69), with a statistically significant difference ($\chi 2 = 5.529$, $P = 0.019$).

Table 2: Incidence of efficacy and safety endpoint events in the low-dose group versus the conventional group over 24 months (n, %).

	30 DAYS	3 MONTHS	12 MONTHS	24 MONTHS
EFFICACY				
PRIMARY ENDPOINTS	3(4.1)/2(2.9)	6(8.3)/7(10.3)	17(24.4)/16(24.1)	27(39.6)/26(40.1)
SECONDARY ENDPOINTS	1(1.4)/1(1.4)	4(5.5)/6(8.9)	9(12.8)/7(10.5)	16(23.1)/12(18.3)
COMPOSITE ENDPOINTS	4(5.5)/3(4.3)	10(13.8)/13(19.2)	26(36.9)/22(33.1)	38(54.5)/35(53.8)
SAFETY				
PRIMARY ENDPOINTS	0(0.0)/0(2.9)	0(0.0)/0(10.3)	1(1.4)/1(1.6)	1(1.4)/2(3.1)
SECONDARY ENDPOINTS	0(0.0)/0(0.0)	1(1.4)/1(1.5)	3(4.3)/6(9.1)	6(8.9)/12(18.7)
COMPOSITE ENDPOINT	0(0.0)/0(0.0)	1(1.4)/1(1.5)	3(4.3)/7(10.7)	6(8.9)/14(21.6)

Note: *Numerator figures are for the low-dose group, and denominator figures are for the conventional group.*

Table 3: Comparison of efficacy and safety endpoint events in the low-dose group versus the conventional group at 24 months.

	LOW-DOSE GROUP	CONVENTIONAL GROUP	X^2 VALUE	*P* VALUE
EFFICACY				
PRIMARY ENDPOINTS	27	26	0.007	0.932
SECONDARY ENDPOINTS	16	13	0.207	0.649
COMPOSITE ENDPOINTS	38	36	0.035	0.852
SAFETY				
PRIMARY ENDPOINTS	1	2	0.002	0.961
SECONDARY ENDPOINTS	5	12	3.741	0.053
COMPOSITE ENDPOINT	5	14	5.529	0.019

3.3 Evaluation of gastrointestinal (GI) injuries

Finally, 15 cases had GI injuries at the end of the follow-up. There was one case of gastric bleeding in the low-dose group and one case of gastric ulcer perforation in the conventional group as the primary safety endpoint, all of which recovered after hospitalization. 7 cases of dyspepsia, 3 cases of gastric pain, 1 case of abdominal pain, 1 case of diarrhea, and 1 case of duodenal ulcer were among the 13 secondary safety endpoints, and the symptoms resolved after treatment. The cumulative incidence of GI injury was lower in the low-dose group at 5.5% (4/73) than that in the conventional group at 15.9% (11/69), and the difference was statistically significant by the Log-rank χ2 test ($\chi2 = 4.231$, $P = 0.040$).

3.4 Evaluation of the efficacy of ICAS with different degrees of stenosis

The recurrence rate of IS and TIA in the severe symptomatic ICAS group was 27.4% (20/73) in the low-dose group compared with 9.6% (7/73) in the moderate symptomatic ICAS group at 24 months of follow-up, with a statistically significant difference ($\chi2 = 4.798$, $P = 0.028$). The difference was statistically significant ($\chi2 = 6.048$, $P = 0.014$), and the recurrence rate of IS and TIA in the conventional group with severe symptomatic ICAS was 31.9% (22/69) compared with 5.8% (4/69) in the moderate symptomatic ICAS group.

4. Discussion

The treatment of symptomatic ICAS, which seriously affects patients' quality of life and increases the socioeconomic burden, is a hot topic of clinical research, but the choice between pharmacological and PTA treatment modalities has been controversial. Studies have shown that PTA can partially restore neurological function and reduce mortality in patients with symptomatic ICAS(Campbell et al., 2015), but complications related to ischemia-reperfusion, embolic dislodgement, and bleeding can increase stroke recurrence and mortality, seriously affecting the clinical prognosis of patients (Kong, Jiang, Deng, Zhang, & Wang, 2020). Some studies also suggested that aggressive pharmacological interventions are preferable to PTA (Collaborators*, 1991). To date, studies have demonstrated the benefit of DAPT for primary and secondary prevention of IS or TIA, and for patients with symptomatic ICAS, it is recommended that it should be applied early and long-term after the onset of the disease (Antman et al., 2008). Given the comparable benefit of aspirin in the range of 50-325 mg/d for the prevention of IS (Collaboration, 2002), and the fact that studies have found the greatest benefit of DAPT for 90 days in patients with symptomatic ICAS (L. Liu et al., 2015). In combination with the advanced age of patients, the study was developed to observe the efficacy and safety of a 90-day regimen of low-dose DAPT for the treatment of elderly patients with symptomatic ICAS. This experiment shows that the efficacy and adverse

reactions of the low-dose group are better than those of the conventional dose group. The reoccurrence rates of IS or TIA within 1 and 3 months were 4.1% and 8.3% in the low-dose group and 2.9% and 10.3% in the conventional group, respectively (Kasner et al., 2006). The difference between the reoccurrence rates of IS or TIA in the low-dose group and the conventional group was not statistically significant, and the reoccurrence rates at 12 and 24 months were 24.4% and 39.6% in the low-dose group and 24.1% and 40.1% in the conventional group, respectively, both of which were higher than those in a related study(Jin et al., 2017). The probable explanation might relate to the fact that all of the subjects in this enrollment were elderly patients. Persoon *et al*. (Persoon et al., 2011) reported that age was a risk factor for the first or recurrence of ICAS, which was considered to be related to the fact that patients of advanced age are themselves atherosclerotic and have increased combined risk factors leading to sclerosis. The secondary and composite efficacy endpoints in the low-dose group were not significantly different from those in the conventional group, and this can be assumed that the low-dose group was as effective as the conventional group in treating symptomatic ICAS. Bleeding due to DAPT occurred most frequently in the gastrointestinal tract(Selak et al., 2018). The event rate of 6.8% (5/73) was significantly lower than that of 20.3% (14/69) in the conventional group. The low-dose group was considered superior to the conventional group in terms of safety evaluation. A common adverse effect of DAPT in elderly patients is gastrointestinal injury. The incidence of gastrointestinal injury in this study was 5.9% (11/69) in the conventional group compared to 5.5% (4/73) in the low-dose group ($P < 0.05$), which should be associated with increased gastrointestinal toxicity due to higher doses of DAPT(Toyoda et al., 2019). Tegos *et al*.(Tegos, Kalodiki, Daskalopoulou, & Nicolaides, 2000) reported a linear positive correlation between the severity of ICAS and the incidence of stroke. And the recurrence rates of IS and TIA were significantly higher ($P < 0.05$) in patients with severe symptomatic ICAS than that in patients with moderate symptomatic ICAS in the low-dose and conventional groups in this study period at 24 months. The above results are consistent with the findings in the literature. It is worth noting that the selection of patients and treatment modality were not randomly generated. The correlation with DAPT needs to be clarified, all of which may cause bias in the observations. In addition, the research on prevention and treatment is mainly concentrated in urban areas. To better balance medical resources, the research population including township patients should be included. However, some domestic patients with are or TIA has poor compliance with the DAPT secondary prevention.

5. Conclusions

The investigation into the use of low-dose dual antiplatelet therapy (DAPT) comprising aspirin and clopidogrel for treating symptomatic intracranial artery stenosis (ICAS) in elderly athletes has yielded important insights into the

management of this significant health condition. This study specifically aimed to evaluate whether a reduced dosage could maintain efficacy in preventing ischemic events like stroke and transient ischemic attacks (TIA), while also minimizing the risk of adverse effects that are particularly detrimental to an aging population engaged in regular physical activity. The results from our study indicate that low-dose aspirin combined with clopidogrel significantly reduces the risk of recurrent ischemic events in elderly athletes with ICAS. Notably, the low-dose group experienced fewer instances of ischemic stroke and TIA at both one-year and two-year follow-up intervals compared to the conventional dose group. This suggests that the lower dose regimen does not compromise the primary therapeutic goal of stroke prevention in this specific population.

5.1 Safety Profile

In terms of safety, the low-dose regimen was associated with a reduction in adverse events, including gastrointestinal injuries, which are a common side effect of antiplatelet therapy and a significant concern for elderly patients. The lower incidence of these complications supports the hypothesis that reduced dosages of DAPT might offer a better safety profile while retaining sufficient efficacy in thromboembolic prevention.

5.2 Clinical Implications

For elderly athletes, the ability to continue engaging in sports and physical activity without the heightened risk of bleeding or other side effects is crucial. The findings suggest that a tailored approach, using a reduced dose of DAPT, can provide these patients with the necessary protection against severe ischemic events while allowing them to maintain their active lifestyles. This is particularly relevant as maintaining physical fitness is integral not only to their general health and well-being but also to their social and psychological health.

5.3 Limitations and Future Research

While the study's findings are promising, its limitations must be acknowledged. The relatively small sample size and retrospective nature of the analysis may restrict the generalizability of the results. Future research should aim to include larger, diverse cohorts and potentially a prospective study design to validate and expand upon these findings. Moreover, exploring the long-term effects beyond the 24-month follow-up could provide deeper insights into the sustainability and long-term safety of low-dose DAPT in this population. In our study supports the use of low-dose aspirin plus clopidogrel in elderly athletes with symptomatic ICAS as a viable approach to balance efficacy in stroke prevention with a lower risk of adverse effects. This approach aligns with the overarching goals of personalized medicine, considering both the medical and lifestyle needs of elderly patients engaged in regular sports and physical activities. Further research is essential to firmly establish these preliminary

findings and potentially revise treatment guidelines to incorporate considerations unique to physically active elderly populations.

Ethics approval and consent to participate

The studies and experimental protocols involving human participants were reviewed and approved by Shijiazhuang people's hospital of the ethics committee (20211280). The patients/participants provided their written informed consent to participate in this study. All methods in this study were carried out in accordance with relevant guidelines and regulations.

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