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ORIGINAL ARTICLE

Safety and Efficacy of Low-dose Prasugrel in the Endovascular Treatment of Unruptured Aneurysms in the Elders (≥ 75 Years)

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Abstract

Purpose The effectiveness and safety of low-dose prasugrel (PSG) premedication for endovascular treatment of unruptured intracranial aneurysms (UIAs) have been widely reported. In this study, we evaluated the clinical outcomes of elders patients (≥ 75 years) treated with PSG.

Methods A total of 200 patients with 209 UIAs who were administered PSG as premedication (20 mg loading and 5 mg maintenance with 100 mg aspirin) between March 2018 and December 2021 were retrospectively enrolled. Among them, 39 patients were aged 75 years or over (elders group), and 161 patients were aged under 75 years (control group). Patients' clinical data were collected, and outcomes were compared between the two groups.

Results Of the 200 patients with PSG, 9 cases (4.5%) had overall complications (7 ischemic, 2 hemorrhagic). In the comparison between the elders group and the control group, no significant differences were observed in the overall complication rates (elders group vs. control group; 2.6% vs. 5.0%, $P = 1.00$). Moreover, the rates of poor clinical outcome were comparable (2.6% vs. 1.2%, $P = 0.48$). The subgroup analysis of patients with stent-assisted procedures revealed no significant differences in complication rates (0% vs. 1.6%, $P = 1.00$) or poor clinical outcomes (0% vs. 0%, $P = 1.00$) during maintenance with aspirin 100 mg or PSG 5 mg.

Conclusion The complication rates in the elders treated with low-dose PSG premedication were similar to those in the control. Low-dose PSG premedication could be prescribed without any additional risk for the endovascular treatment of UIAs in elders patients.

Keywords Dual anti-platelet therapy · Coil embolization · Premedication · Dual anti-platelet therapy · Thienopyridines · Aged

Introduction

The preference for endovascular treatment for unruptured intracranial aneurysms (UIAs) is increasing especially in elders patients with its proven safety and efficacy [1, 2]. Given the nature of the endovascular treatment, which is carried out within blood vessels, there is a risk of thromboembolism due to the instrument itself or changes in blood flow after the procedure. Therefore, preventive medical management in the periprocedural period is essential to minimize complications. Although dual antiplatelet treatment (DAPT) with acetylsalicylic acid (aspirin) and clopidogrel (CPG) is widely used for the premedication of endovascular treatment, variability in patient responses has caused increasing concern about the effectiveness of CPG [3]. Hence, premedication with prasugrel (PSG) was proposed as an alternative [4]. A third generation thienopyridine, PSG, provides more predictable and consistent inhibition of adenosine diphosphate (ADP)-induced platelet aggregation than CPG.

In general, PSG was not prescribed for acute coronary syndrome (ACS) patients aged 75 years or older due to the bleeding risk and uncertain benefits [5]; however, a low-dose PSG regimen has been reported to be safe to treat ACS in patients older than 75 years [6]. Low-dose PSG premedication (20 mg loading and 5 mg maintenance) during the endovascular treatment of UIAs also showed excel-

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lent safety and effectiveness [7–10]; however, the experiences with low-dose PSG premedication for the endovascular treatment of patients older than 75 years have not yet been reported. In this retrospective study, we compared the clinical outcomes of low-dose PSG premedication in patients older than 75 years and those aged under 75 years.

Methods

Study Population

Between March 2018 and December 2021, endovascular treatment was performed for 484 intracranial aneurysms in 469 patients at our institution. Of these, 186 acutely ruptured aneurysms in 182 patients and 89 aneurysms in 87 patients who had taken periprocedural antiplatelet medication other than PSG were excluded from the study. A total of 209 aneurysms from 200 patients were finally included, and the subjects were divided into two groups according to the criterion of age 75 years and analyzed. The group of patients aged 75 years and over (elders group) included 42 aneurysms in 39 patients, and the group of patients aged under 75 years (control group) included 167 aneurysms in 161 patients (Fig. 1). This study was approved by the Institutional Review Board, according to principles outlined in the Helsinki Declaration (approval No. 2101-013-19351). Informed consent was waived due to the retrospective nature of this study.

Data Collection

We performed a retrospective review of consecutive patients who received endovascular treatment for UIAs after periprocedural antiplatelet medication with PSG. The data were extracted from electronic medical records in an institutional database using a standardized data collection form. The baseline medical variables of the patients, including sex, age, and body mass index, were collected. The medical and social histories of patients, including hypertension, diabetes mellitus, alcohol, smoking, and cerebrovascular disease were reviewed, and the patients' prior medications, including antiplatelets, anticoagulants, and statins, were recorded. Additionally, laboratory data, including platelet count, activated partial thromboplastin time, prothrombin time, high-density lipoprotein, low-density lipoprotein (LDL), triglycerides, and total cholesterol level were collected.

Clinical data on aneurysms and endovascular treatment were also collected. The aneurysmal configuration and arterial architecture of each aneurysm were measured based on cerebral angiography and rotational angiography with 3D image reconstruction using the AXIOM Artis dBA or AXIOM Artis Q system (both Siemens AG, Forchheim, Germany). Aneurysm data, including maximum diameter, dome-to-neck ratio, volume, and location, were collected.

Clinical data of endovascular treatment included loading and maintenance doses of the administered PSG and platelet function test values, such as aspirin reaction units (ARUs), P2Y12 reaction units (PRUs), and percentage inhibition rate. Whether the procedure was a reoperation was noted, and the type of treatment modality, packing density, and degree of occlusion were recorded. The coil packing density was calculated as the ratio of the volume of the deployed coils to the volume of the aneurysm. The degree of occlusion was categorized according to the Raymond classification.

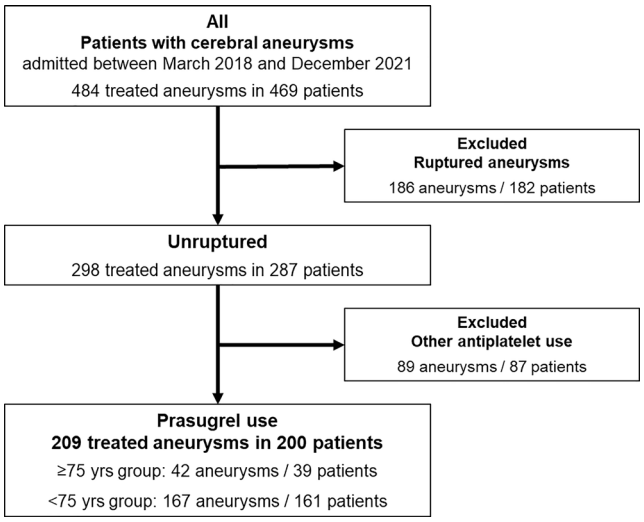

Fig. 1 Flow diagram of inclusion and exclusion criteria

Periprocedural Antiplatelet Medication and Endovascular Procedure

The loading dose of antiplatelet medication was administered the day before the procedure. Dual antiplatelet medications (100 mg aspirin with 20 mg PSG) were given. An additional 5 mg PSG and 100 mg aspirin were given on the morning of the procedure. The VerifyNow assay (Accumetrics, San Diego, CA, USA) was used to measure platelet reactivity. Whole blood was obtained 6 h after loading with antiplatelet medication, and ARU, PRU, and percentage inhibition values were measured. Patients with PRU values greater than 285 were defined as poor responders and given an additional 10 mg of PSG.

All procedures were performed with the patient under general anesthesia in a neuroangiography suite using a standardized protocol. The endovascular technique was appropriately chosen and performed after being discussed by the neurosurgery and neurointervention team. Systemic heparinization was conducted upon initiation of the procedure.

Heparinized saline flush lines were used at a concentration of 5 IU/mL in normal saline. A bolus of 3000 IU heparin was given after the femoral sheath insertion, followed by an intermittent bolus of 1000 IU every hour with monitoring of the activated clotting time. The target activated clotting time was 250–300 s.

We advised the use of DAPT (5 mg prasugrel and 100 mg aspirin) for a minimum of 1 month after stent-assisted coil embolization (SAC), and to keep it for 3 months if possible, followed by life-long maintenance on aspirin for the patients undergoing stent implantation; however, the antiplatelet therapy regimen was tailored to the patient considering the patient's procedural thromboembolic complications, underlying diseases, prior antiplatelet agent use, side effects, and compliance.

Procedure-related Complications

Thromboembolism was defined as thrombus formation and/or distal embolism observed during the procedure (intraprocedural thromboembolism) or clinically recognized transient or fixed ischemic deficits that occurred during the PSG prescription. Intraprocedural thromboembolic complications were diagnosed when there was a luminal filling defect, stagnation of the contrast filling of a vessel, or nonvisualization of a distal artery. When thromboembolism was detected, tirofiban (a short-acting glycoprotein IIb/IIIa antagonist) was given intra-arterially or intravenously. Angiography was performed to assess the clotting status and arterial flow. When clot resolution was achieved, angiography was performed once more 10 min later. When the thrombus remained after infusion or delayed clot formation was expected, intravenous infusion of tirofiban ($0.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$) was maintained for up to 12 h after the embolization procedure.

Hemorrhagic complications were defined as clinically recognized hemorrhagic events occurring during the PSG prescription. Intracranial hemorrhagic complications included events such as intraprocedural aneurysm leakage, delayed aneurysm rupture, and intracerebral hemorrhage. Extracranial hemorrhagic complications were defined as bleeding corresponding to the major or minor criteria of the Thrombolysis In Myocardial Infarction (TIMI) bleeding criteria, the most common classification used to report bleeding severity after antiplatelet therapy [11]. All patients were instructed to visit the emergency center or contact the neurointerventional team by telephone if any neurological symptoms or bleeding events occurred. The clinical outcomes of the patients with complication events were assessed in an independent outpatient clinic according to a modified Rankin scale (mRS) score 6 months after the procedure. Poor clinical outcome was defined as mRS ≥ 2 at 6 months postprocedure.

Statistical Analyses

Categorical variables were expressed as frequencies and percentages. We used χ^2-test or Fisher's exact test to analyze categorical variables using contingency tables. Continuous variables were expressed as the mean ± standard deviation. The mean differences between the groups were analyzed using Student's t-test when variables were normally distributed. For non-normally distributed variables, the Mann-Whitney *U* test was used. $P < 0.05$ was considered statistically significant. IBM SPSS Statistics for Windows (version 23; IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 8; Graph Pad Software Inc., San Diego, CA, USA) were used for all statistical analyses.

Results

Enrolled Patients and Aneurysms

The baseline characteristics of patients and laboratory data are shown in Table 1. The two groups differed significantly regarding the history of hypertension, diabetes mellitus, alcohol, and ischemic stroke. A comparison of the laboratory data revealed significant differences in the platelet count, LDL level, and total cholesterol level.

The two groups exhibited similar characteristics of treated aneurysms in terms of size and location. Moreover, a comparison of the endovascular treatment data revealed no significant difference. PRU values were comparable between the two groups (elders group vs. control group, 133.0 ± 92.3 vs. 126.6 ± 89.1; $P = 0.692$), as were percentage inhibition values (elders group vs. control group, 53.2 ± 31.1 vs. 52.5 ± 32.0; $P = 0.894$). The two groups were also comparable in terms of treatment modality, packing density, and degree of occlusion.

Clinical Outcome with Prasugrel

In this cohort of 200 patients who underwent endovascular treatment, a total of 9 cases (4.5%) had procedure-related complications 7 patients (3.5%) suffered thromboembolic events, and 2 patients (1.0%) had hemorrhagic events (Table 2). The comparison of the overall complication rates between the two groups revealed no significant differences (2.6% vs. 5.0%; $P = 1.000$). The hemorrhagic complications (0% vs. 1.2%; $P = 1.000$) and thromboembolic complications (2.6% vs. 3.7%; $P = 1.000$) were comparable between the two groups. Moreover, the rates of poor clinical outcomes were similar (2.6% vs. 1.2%; $P = 0.480$) (Table 3). In addition, when the clinical data of the patients who underwent a SAC were compared, no significant differences were found between the elders group and the control group.

Table 1 Baseline characteristics of patients, laboratory data, and aneurysms

Variables	Elders group (≥ 75 years, $n = 39$)	Control group (< 75 years, $n = 161$)	P-value
Female	33 (84.6%)	113 (70.2%)	0.074
Age (years)	78.7 ± 3.1	59.3 ± 10.4	**< 0.001**
Body mass index (kg/m^2)	24.9 ± 3.4	24.7 ± 3.5	0.761
Medical and social history			
Hypertension	31 (79.5%)	74 (46.0%)	**< 0.001**
Diabetes mellitus	11 (28.2%)	21 (13.0%)	**0.028**
Alcohol	3 (7.7%)	54 (33.5%)	**< 0.001**
Smoking	5 (12.8%)	43 (26.7%)	0.093
Ischemic stroke	5 (12.8%)	6 (3.7%)	**0.041**
Intracerebral hemorrhage	1 (2.6%)	5 (3.1%)	1.000
Subarachnoid hemorrhage	4 (10.3%)	34 (21.1%)	0.171
Prior medication			
Antiplatelet	12 (30.8%)	30 (18.6%)	0.124
Anticoagulant	3 (7.7%)	9 (5.6%)	0.706
Statin	20 (51.3%)	63 (39.1%)	0.205
Laboratory data			
Platelet count (×10^3/μL)	219.5 ± 63.5	249.0 ± 59.4	**0.007**
aPTT (s)	30.0 ± 3.2	31.0 ± 3.7	0.101
PT (INR)	1.0 ± 0.1	1.0 ± 0.1	0.395
HDL (mg/dL)	50.4 ± 12.8	52.8 ± 12.3	0.339
LDL (mg/dL)	86.1 ± 28.7	106.2 ± 30.3	**< 0.001**
Triglyceride (mg/dL)	120.0 ± 61.2	153.3 ± 105.1	0.087
Total cholesterol (mg/dL)	154.3 ± 41.1	182.9 ± 42.7	**< 0.001**
Aneurysm data			
Maximum diameter (mm)	5.7 ± 2.9	5.1 ± 2.9	0.199
Dome to neck ratio	1.4 ± 0.3	1.4 ± 0.4	0.875
Volume (mm3)	191.8 ± 522.6	110.1 ± 302.9	0.196
Location			
Internal carotid artery	22 (52.4%)	77 (47.6%)	0.493
Anterior cerebral artery	7 (16.7%)	53 (31.7%)	0.058
Middle cerebral artery	9 (21.4%)	25 (15.0%)	0.350
Posterior circulation	4 (9.5%)	12 (7.2%)	0.534
Prasugrel dose (loading/maintenance, mg)			0.256
20/5	33 (84.6%)	146 (90.7%)	
30/5	6 (15.4%)	15 (9.3%)	
Platelet function test			
ARU	492.7 ± 82.9	503.3 ± 83.6	0.500
PRU	133.0 ± 92.3	126.6 ± 89.1	0.692
Percentage inhibition (%)	53.2 ± 31.1	52.5 ± 32.0	0.894
Reoperation	4 (9.5%)	25 (15.0%)	0.460
Treatment modality			
Single microcatheter	12 (28.6%)	47 (28.1%)	1.000
Double microcatheter	12 (28.6%)	53 (31.7%)	0.852
Stent assisted	16 (38.1%)	61 (36.5%)	0.860
Balloon assisted	1 (2.4%)	5 (3.0%)	1.000
Flow-diverter	1 (2.4%)	1 (0.6%)	0.362
Packing density (%)	27.1 ± 6.2	29.3 ± 7.4	0.108

Table 1 (Continued)

Variables	Elders group (≥ 75 years, *n* = 39)	Control group (< 75 years, *n* = 161)	P-value
Occlusion			
Complete	21 (50.0%)	76 (45.5%)	0.609
Residual neck	19 (45.2%)	77 (46.1%)	1.000
Residual sac	2 (4.8%)	14 (8.4%)	0.745

aPTT activated partial thromboplastin time, *PT* prothrombin time, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ARU* aspirin reaction unit, *PRU* P2Y12 reaction unit

Table 2 Clinical data of patients with procedure-related adverse events

No	Group	Location	Technique	PRU	Percentage inhibition (%)	Prasugrel dose (loading/maintenance, mg)	Event	mRS[a]
1	Elders	MCA	Double microcatheter	92	70	20/5	Delayed infarction in 3 weeks at left frontal lobe, insula, and basal ganglia	3
2	Control	VA	Double microcatheter	242	25	20/5	Delayed focal infarction in 4days at PICA territory	2
3	Control	PCoA	Double microcatheter	162	30	20/5	Left side motor weakness grade IV with multifocal diffusion restricted lesion at immediate post-operative	1
4	Control	ACoA	Single microcatheter	29	89	20/5	Puncture site hematoma after successful suture-mediated closure (Hb dropped from 14 to 8 g/dL)	0
5	Control	ACoA	Double microcatheter	318	3	30/5	Delayed ACA infarction in 8 days	4
6	Control	MCA	Single microcatheter	28	87	20/5	Small ICH at immediate post-operative	0
7	Control	ACoA	Stent assisted	114	58	20/5	In-stent thrombosis during coiling	0
8	Control	PCA	Stent assisted	9	97	20/5	In-stent thrombosis during coiling	0
9	Control	PCoA	Stent assisted	207	18	20/5	Hypoesthesia in right hand with multiple cortical and subcortical diffusion restricted lesions in post-op 1 day	1

PRU P2Y12 reaction unit, *mRS* modified Rankin Scale, *MCA* middle cerebral artery, *VA* vertebral artery, *PICA* posterior inferior cerebellar artery, *PCoA* posterior communicating artery, *ACoA* anterior communicating artery, *Hb* hemoglobin, *ACA* anterior cerebral artery, *ICH* intracerebral hemorrhage, *PCA* posterior cerebral artery

[a]mRS score at postprocedural 6 months

Table 3 Comparison of procedure-related adverse events

Complications	Elders group (≥75 years, *n* = 39)	Control group (<75 years, *n* = 161)	P-value
Overall complication	1 (2.6%)	8 (5.0%)	1.000
Hemorrhagic complication	0 (0%)	2 (1.2%)	1.000
Thromboembolism	1 (2.6%)	6 (3.7%)	1.000
Poor clinical outcome[a]	1 (2.6%)	2 (1.2%)	0.480

[a]mRS score of ≥ 2 at 6 months postprocedure

Table 4 Comparison of procedure-related adverse events with stent-assisted aneurysm treatment

Variables	Elders group (≥75 yrs , $n=16$)	Control group (<75 yrs, $n=62$)	P-value
Platelet function test			
ARU	536.5 ± 82.5	503.5 ± 78.7	0.177
PRU	129.3 ± 87.1	129.8 ± 84.7	0.985
Percentage inhibition (%)	54.6 ± 30.5	50.8 ± 30.9	0.672
Duration of prasugrel administration (days)	43.3 ± 43.1	66.7 ± 61.5	0.183
Overall complications[a]	0 (0%)	1 (1.6%)	1.000
Hemorrhagic complication	0 (0%)	0 (0%)	1.000
Thromboembolism	0 (0%)	1 (1.6%)	1.000
Poor clinical outcome	0 (0%)	0 (0%)	1.000

ARU aspirin reaction unit, *PRU* P2Y12 reaction unit
[a]From the day after the procedure

The comparison of the overall complication rates revealed no significant differences between the two groups (0% vs. 1.6%, $P=1.00$), and no poor clinical outcomes occurred in either group over a mean period of 62.2 ± 58.9 days (median 46 days; range 1–365 days) (Table 4).

Discussion

This study compared the clinical outcomes of endo for UIAs with low-dose PSG between patients ≥ 75 years and < 75 years of age. The elders (aged ≥ 75 years) showed similar results in terms of hemorrhagic complications, thromboembolisms, and clinical outcomes compared with those aged < 75 years.

With the remarkable advances in devices and techniques, endovascular treatment is gradually becoming safer. Nevertheless, because thromboembolic complications still cause neurointerventionalists great concern, pretreatment using DAPT has become the standard treatment for the prevention of thromboembolic complications [12]. In general, DAPT with aspirin and CPG is widely used; however, a method using PSG, a third generation thienopyridine, is also emerging due to variability in responses to CPG [4]. The differences in metabolism lead to PSG considerably rapid and consistent response, and it has been utilized as an alternative in patients with CPG resistance [13].

Due to these differences in pharmacokinetics and pharmacodynamics, PSG has been prescribed for patients with cardiovascular treatment as an alternative to CPG [14]. Nevertheless, TRITON-TIMI 38 trial found a higher risk of fatal bleeding events (1.0%) in elders (aged ≥ 75 years) patients treated with PSG than in those treated with CPG [5]. Moreover, as the effectiveness of PSG is uncertain in patients ≥ 75 years of age, PSG is generally not prescribed for these patients; however, recent guidelines for chronic coronary syndrome recommended PSG as a DAPT treatment option for patients with post-percutaneous coronary intervention for myocardial infarction who have tolerated DAPT for 1 year, with a reduced dose of 5 mg PSG in patients ≥ 75 years of age [13]. The PRASTRO-II study also reported similar safety and a lower incidence of ischemic stroke and myocardial infarction with PSG 3.75 mg than in those with CPG 75 mg in elders patients with previous ischemic stroke [6]. In line with previous research 5 of 39 patients had suffered previous stroke, but hemorrhagic complications did not occur in any of these patients in the current study.

In an previous study of PSG in neurointerventional procedures, PSG (60 mg loading and 10 mg maintenance) showed significantly higher rates of hemorrhagic complications than 75 mg CPG [15]; however, a low-dose PSG regimen with 20 mg (corresponding to one third of the TRITON-TIMI 38 trial) loading the day before a procedure and a 5 mg maintenance dose (half of the trial dose) on the morning of a procedure, was applied to reduce the risk of hemorrhage during endovascular treatment for cerebral aneurysms. This regimen effectively reduced thromboembolic events with an acceptable rate of hemorrhage complications [7–9, 16]. Tailored low-dose PSG for the poor responder with CPG premedication also prevents effect of thromboembolism without increased risk of hemorrhage [17–19]. Moreover, low-dose PSG proved the feasibility in flow-diverting stent implantation as a first-line therapy and rescue therapy for the CPG hyporesponders [20, 21].

To our knowledge, this study is the first report in the neurointerventional field on low-dose PSG premedication in patients ≥ 75 years of age. Considering the low rupture risk of UIAs and the life expectancy of the elders, careful consideration is needed in selecting patients who will undergo treatment for UIAs. In addition, atherosclerosis in the elders raises concerns about thromboembolisms and, at the same time, requires consideration of the bleeding risk of DAPT. In line with a previous study [22] responses to PSG were comparable in the current study (elders group vs. control group, 133.0 ± 92.3 vs. 126.6 ± 89.1 PRU, $P=0.692$).

Although the two groups differed on several baseline characteristics due to the age difference, the overall complication rates, including hemorrhagic complications and thromboembolisms, were comparable between the two groups. In particular, no hemorrhagic complications occurred in the elders group, and the elders patients with a stent ($n = 16$) were also safe during maintenance with 100 mg aspirin and 5 mg PSG (mean period, 43.3 ± 43.1 days). Moreover, poor clinical outcomes were also similar between the two groups. These results suggest that the thromboembolic risk in endovascular treatment of UIAs could be minimized without increasing the bleeding risk in the elders ≥ 75 years of age.

Several limitations of this study should be considered when interpreting the results. First, this study was retrospective in nature. Second, there were fewer subjects in the elders group than in the control group, as the age range of the included subjects was narrow, and the treatment was strictly selected in consideration of the age and medical condition of the elders. A larger prospective randomized multicenter trial should be performed to clarify the safety and effectiveness of low-dose PSG premedication in the elders and to obtain the optimal guideline.

Conclusion

Low-dose PSG premedication showed similar safety and effectiveness in the elders (≥ 75 years of age) and the control groups. Therefore, low-dose PSG premedication for endovascular treatment of UIAs could be prescribed to the elders without increasing the risk of bleeding.

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Conflict of interest S.H. Lee, H.H. Choi, K. Min Jang, T. Kyun Nam and J. Soo Byun declare that they have no competing interests.

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