Tropical Journal of Pharmaceutical Research December 2021; 20 (12): 2605-2610
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i12.21

Original Research Article

Comparative study on the clinical efficacy of clopidogrel and ticagrelor in patients with stent-assisted aneurysm embolization

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Sent for review: 19 June 2021 *Revised accepted: 29 November 2021*

Abstract

Purpose: *To investigate the clinical efficacy and safety of clopidogrel and ticagrelor in stent-assisted aneurysm embolization.*
Methods: *One hundred and ten patients with stent-assisted embolization of intracranial aneurysms were randomized into control and study groups (CG and SG). CG received clopidogrel plus aspirin while SG received ticagrelor plus aspirin Their clinical efficacies were compared.*
Results: *The maximum platelet aggregation rate (MPAR) and P2Y12 reaction unit (PRU) at 24 h and 1 week after surgery in SG were significantly lower compared with CG ($p < 0.05$). Arachidonic acid (AA) inhibition rate in SG was slightly higher than that in CG ($p > 0.05$), while the adenosine diphosphate (ADP) inhibition rate in SG was higher compared with CG ($p < 0.05$). The inflammatory factor levels were significantly lower in SG than in CG ($p < 0.05$). The incidence of clinical endpoint events within one year after surgery in SG was notably lower compared with CG ($p < 0.05$).*
Conclusion: *For patients with stent-assisted aneurysm embolization, ticagrelor has a better inhibitory effect on platelet aggregation and a lower incidence of platelet resistance than those of clopidogrel. In addition, ticagrelor inhibits the occurrence of clinical endpoint events and has high medication safety.*

Keywords: *Clopidogrel, Ticagrelor, Stent implantation, Intracranial aneurysms*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Intracranial aneurysms are saccular aneurysms formed by the outward expansion of the internal cerebral arterial wall under the influence of some factors, which are highly prone to sudden rupture when blood pressure increases. Then intracranial subarachnoid hemorrhage or other serious complications are caused, greatly harming the health and safety of patients [1-4]. Intracranial stent-assisted embolization is one of the main methods for treating intracranial aneurysms in China, and patients are usually given dual anti-platelet plans (oral clopidogrel combined with aspirin or ticagrelor combined with aspirin) before surgery, during surgery and after surgery to prevent thrombosis [5-8]. Regarding the treatment of intracranial vascular diseases, there

are few literature on the effect comparison between clopidogrel and ticagrelor, with few reports on the guidelines for the treatment of related diseases. Based on this, this study will apply the thromboelastography (TEG) to detect the platelet inhibition rate, and compare the antiplatelet effect and safety between clopidogrel and ticagrelor, aiming to further guide the clinical application of antiplatelet drugs in intracranial stent-assisted embolization.

METHODS

General profile of patients

The 110 patients with stent-assisted embolization of intracranial aneurysms admitted to the Neurosurgery Department of Rushan People's Hospital (January 2017 - December 2020) were equally randomized into control group (CG) and study group (SG). CG received clopidogrel plus aspirin while SG received ticagrelor plus aspirin. No statistical significance in patients was observed between the two groups ($p > 0.05$), as presented in Table 1. The study was conducted in accordance with the Declaration of Helsinki as revised in 2013 [9]. This study received the approval of the Ethics Committee of Rushan People's Hospital (approval no. rs202102), and the patients/families gave their informed consent.

Inclusion criteria

The patients met the clinical diagnostic criteria of intracranial aneurysms and had the indications for stent-assisted embolization; the patients were aged 18 - 75 years old; and the patients did not take antiplatelet drugs via P2Y12 pathway in the past week.

Exclusion criteria

The patients were allergic to aspirin, clopidogrel and ticagrelor; the patients used other antiplatelet drugs except aspirin, clopidogrel and ticagrelor during treatment; the patients had hematological diseases, hemorrhagic diseases or bleeding tendency; the patients had active upper gastrointestinal ulcer or a history of upper gastrointestinal tract perforation and intracranial hemorrhage; the patients had grade IV of cardiac function, or severe hepatic and renal dysfunction; the patients had severe infection, malignant tumors and rheumatic immune system diseases; and The patients took strong CYP3A4 inhibitors such as nefazodone, itraconazole, clarithromycin, saquinavi and atazanavir.

Treatments

CG received clopidogrel plus aspirin. On the day of admission, the patients were given aspirin (specification: 100 mg; manufacturer: Bayer AG; NMPA approval no. J20130078) with a load dosage of 300 mg, and 75 mg of clopidogrel (specification: 75 mg; manufacturer: Sanofi Pharmaceutical Co. Ltd.; NMPA approval no. J20180029). The maintenance doses were 75 mg/day (clopidogrel) and 100 mg/d (aspirin) [10-12].

SG received ticagrelor plus aspirin. On the day of admission, the patients were given aspirin (specification: 100 mg; manufacturer: Bayer AG; NMPA approval no. J20130078) with a load dosage of 300 mg, and 180 mg of Brilinta ticagrelor tablets (specification: 90 mg; manufacturer: AstraZeneca; NMPA approval no. J20130020). The maintenance doses were 90 mg (twice a day for ticagrelor) and 100 mg/day (aspirin). Then thromboelastography was performed. The platelet count of peripheral blood was controlled at 30 x 10^9 - 100 x 10^9 /L, and stent-assisted intracranial aneurysm embolization was performed under general anesthesia [13-15].

Evaluation of treatment indices

Venous blood (4 ml) was extracted before surgery, 24 h after surgery and 1 week after surgery. The PL-11 platelet aggregation analyzer was used to measure the maximum platelet aggregation rate (MPAR), and the Verify Now antiplatelet analyser was used to measure the P2Y12 reaction unit (PRU). 3 mL of venous blood was collected at 5 h after surgery, and placed into a test tube containing 3.13 % of sodium citrate and heparin potassium. Arachidonic acid (AA) and adenosine diphosphate (ADP) were used as activators, respectively.

Table 1: Comparison of baseline data (n = 55)

Item	CG	SG	X^2/t	*P*-value
Male/female	28/27	30/25	0.1459	0.702
Age (years old)	57.6 ± 10.1	57.4 ± 9.8	0.1054	0.9163
Body mass (kg/m^2)	25.39 ± 4.15	25.62 ± 4.23	0.2878	0.7740
Fasting blood glucose (FBS, mmol/L)	7.75 ± 2.02	7.81 ± 2.14	0.1512	0.8801

Then a blood coagulation analyzer (model: TEG5000; manufacturer: Haemoscope, America) was used to detect the platelet inhibition of patients. The serum levels of high-sensitivity C-reactive protein (hs-CRP), interleukin (IL) -6, tumor necrosis factor-α (TNF-α) and matrix metalloproteinase 9 (MMP-9) were measured by double antibody sandwich enzyme-linked immunosorbent assay (ELISA) in the clinical laboratory of our hospital.

Various adverse drug reactions during medication in both groups were recorded, and the adverse cerebrovascular events within one year of follow-up were counted and analyzed.

Statistical analysis

The data obtained were statistically calculated by SAS10.0 software, and graphed by GraphPad Prism 7 software (GraphPad Software, San Diego, USA). The data included enumeration data and measurement data, expressed as [n (%)] and ($\bar{x} \pm s$), and tested by X^2 and t test. The differences were statistically significant at $p < 0.05$.

RESULTS

Platelet aggregation

The MPAR of CG before surgery, 24 h after surgery and 1 week after surgery was 67.47 ± 12.86 59.25 ± 11.23 and 47.69 ± 10.62, while that of SG was 67.62 ± 13.57, 51.14 ± 10.41 and 38.36 ± 9.25. The PRU of CG before surgery, 24 h after surgery and 1 week after surgery was 288.24 ± 14.09, 253.35 ± 13.86 and 208.46 ± 10.25, while that of SG was 289.32 ± 13.33, 208.67 ± 15.18 and 152.13 ± 9.84. The MPAR and PRU at 24 h and 1 week after surgery in SG were markedly lower than those in CG (P < 0.05), see Figures 1-2.

Platelet resistance

The platelet inhibition rates induced by AA and ADP in CG were 89.35 ± 16.33 and 41.43 ± 12.67, while those in SG were 91.27 ± 17.49 and 66.15 ± 15.34, respectively. The AA inhibition rate in SG was slightly higher (P > 0.05), while the ADP inhibition rate in SG was obviously higher compared with CG ($p < 0.05$). See Figure 3.

Inflammatory factor levels

The inflammatory factor levels were markedly lower in SG than in CG ($p < 0.05$), as presented in Table 2.

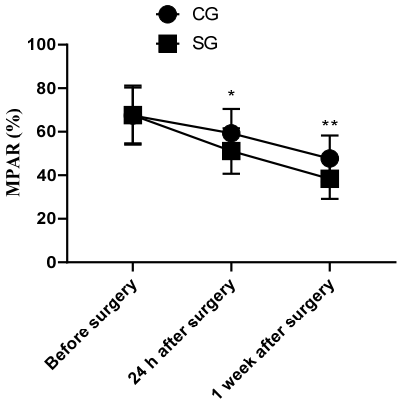

Figure 1: Comparison of MPAR (mean ± SD). * $P < 0.05$, MPAR at 24 h after surgery in CG vs MPAR at 24 h after surgery in SG. ** $P < 0.05$, MPAR at 1 week after surgery in CG vs MPAR at 1 week after surgery in SG

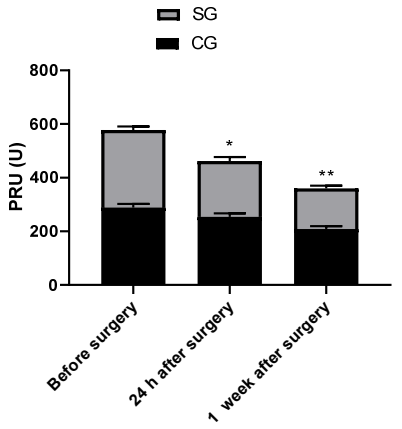

Figure 2: Comparison of PRU (mean ± SD). * $P < 0.05$, PRU at 24 h after surgery in CG vs PRU at 24 h after surgery in SG. ** $P < 0.05$, PRU at 1 week after surgery in CG vs PRU at 1 week after surgery in SG

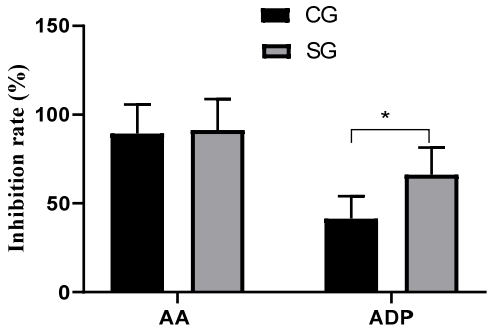

Figure 3: Comparison of platelet inhibition rates (mean ± SD). * < 0.05, ADP-induced platelet inhibition rate in CG vs rate in SG

Table 2: Comparison of inflammatory factor levels (mean ± SD)

Group	hs-CRP (mg/L)	IL-6(ng/L)	TNF-α(ng/L)	MMP-9(ng/L)
CG	5.78 ± 2.24	32.53 ± 9.41	7.26 ± 0.58	71.35 ± 24.58
SG	4.41 ± 1.35	25.71 ± 7.89	6.13 ± 0.36	62.24 ± 19.17
t	3.8848	4.1187	12.2763	2.1674
P-value	0.0002	0.0001	0.000	0.0324

Table 3: Adverse drug reactions [n (%)]

Group	Chest distress	Dyspnea	Gastrointestinal reaction	Total incidence
CG (n = 55)	1(1.82)	2(3.64)	3(5.45)	6(10.91)
SG (n = 55)	1(1.82)	2(3.64)	1(1.82)	4(7.27)
χ^2				0.4400
P-value				0.507

Table 4: Comparison of clinical endpoint events within one year [n (%)]

Event	CG (n = 55)	SG (n = 55)	X^2	*P*-value
Death due to cerebrovascular diseases	3(5.45)	1(1.82)		
Cerebral infarction	1(1.82)	0(0)		
Hematencephalon	3(5.45)	1(1.82)		
Transient ischemic attack	2(3.64)	1(1.82)		
In-stent thrombosis	2(3.64)	0(0)		
Total incidence	11(20)	3(5.45)	5.2381	0.022

Adverse drug reactions

Table 3 presented no notable difference in the incidence of adverse reactions during medication between the two groups ($p > 0.05$).

Incidence of clinical endpoint events

The incidence of clinical endpoint events within one year after surgery was lower in SG than in CG ($P < 0.05$). See Table 4.

DISCUSSION

Stent assistance is an important technique in the intracranial aneurysm interventional embolization. It can achieve good therapeutic effect for the tiny, spindle-shaped and wide-necked intracranial aneurysms that cannot be tightly embolized or even not embolized. It also increases the proportion of embolization, prevent aneurysm recurrence and promote healing [16-19].

Stent assistance have the following advantages in embolization. (a) It can enable the coils to well fill in the tumors, protect the parent arteries and prevent the postoperative cerebral infarction due to stenosis and occlusion of the parent arteries. (b) Due to the obstruction of the stent, the coils in the aneurysmal neck become shaped according to the morphology of the parent arteries, and completely cover the aneurysmal neck. (c) It changes the morphology of parent arteries, guide blood flow, reduce blood flow into the arterial aneurysms and accelerate healing. (d) It stimulates angiogenesis and endothelial growth, thus promoting healing. However, antiplatelet preparation should be made before stent-assisted surgery, and continuous antiplatelet therapy is required after surgery.

Since the most critical treatment node is two months after surgery, which is a crucial moment for vascular endothelialization, effective antiplatelet therapy during this period can greatly reduce the possibility of in-stent thrombosis [20-22]. In fact, there are few studies on the comparison of clopidogrel and ticagrelor in intracranial stent implantation. In order to fill this gap, this paper discusses the antiplatelet efficacy and safety of clopidogrel and ticagrelor when combined with aspirin in stent-assisted aneurysm embolization.

Aspirin plus clopidogrel was once a standard dual anti-platelet aggregation scheme for many cardiovascular and cerebrovascular surgeries, in which the former played an anti-platelet aggregation effect mainly by inhibiting the conversion of arachidonic acid (AA) to thromboxane B2, while the latter selectively inhibits the binding of ADP to other platelet receptors or inhibit the activation of glycoprotein (GP II b/III a) complex, thereby inhibiting platelet aggregation. Ticagrelor and clopidogrel are both receptor antagonists of antiplatelet membrane P2Y12. The difference between them is that

clopidogrel is metabolized through the liver, with possibility of individual differences, while ticagrelor does not need to be activated through liver metabolism but can directly and irreversibly act on P2Y12 receptor, thereby inhibiting ADP-induced platelet aggregation. Compared with clopidogrel, ticagrelor has the advantages of rapid onset, no individual difference, a strong anti-platelet aggregation effect and a low risk of bleeding. Wang *et al* [23] studied the efficacy of clopidogrel and ticagrelor in patients with ACS after PCI, and found that ticagrelor had a lower incidence of clinical endpoint events than clopidogrel, which is in line with this study. This paper confirmed that the incidence of clinical endpoint events within one year after surgery in SG was notably lower than that in CG.

This study also showed that the MPAR and PRU at 24 h and 1 week after surgery in SG were obviously lower than those in CG, suggesting that ticagrelor produced a better antiplatelet effect compared with clopidogrel. The study also concluded that the AA inhibition rate in SG was slightly higher, while the ADP inhibition rate in SG was markedly higher compared with CG, which may be closely related with the metabolic pathways of ticagrelor.

Ticagrelor is active and does not need to be transformed by the liver, thus leading to a stable anti-platelet aggregation effect. The inflammatory factor levels in SG were markedly lower, revealing that ticagrelor has a better effect on reducing the inflammatory factor levels in the arteries. In addition, no obvious difference in the incidence of adverse reactions was observed between the two groups, but the incidence of dyspnea in SG was slightly higher compared with CG, which was mainly due to the effect of ticagrelor adenosine. Guimarães *et al* [24] have mentioned in their study that dyspnea of most patients after oral ticagrelor is mild, and can be alleviated in most patients within seven days and tolerated by patients.

Limitations of the study

The study used a small sample size and short follow-up time. Therefore, more multi-center studies should be carried out to further confirm the efficacy and safety of ticagrelor in patients with stent-assisted aneurysm embolization.

CONCLUSION

For patients with stent-assisted aneurysm embolization, ticagrelor has a better inhibitory effect on platelet aggregation and a lower incidence of platelet resistance than those of clopidogrel. In addition, ticagrelor reduces the levels of arterial inflammatory factor, effectively inhibits the occurrence of clinical endpoint events, and has high medication safety.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Xiao Chen and Weidong Xu designed the study and drafted the manuscript. Lei Zhao and Xiaohui Yue were responsible for the collection and analysis of the experimental data. Yongjun Zhu, Endong Song and Zhiqiang Liu revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. #Xiao Chen and Weidong Xu Contribute equally to this study.

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