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Original Article

The efficacy and safety of carotid stenting under dual antiplatelet therapy with ticagrelor and acetylsalicylic acid*

Tikagrelor ve asetilsalisilik asit ikili antiplatelet tedavisi altında karotis stentlemenin etkinliği ve güvenliği

Ahmet Yabalak

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ABSTRACT

Aim: To prevent thrombotic complications in carotid artery stenting (CAS), it is recommended to use acetylsalicylic acid (ASA) and clopidogrel for at least one month, followed by single antiplatelet therapy. The number of studies on the use of ticagrelor in CAS is very few. We aimed to evaluate the efficacy and safety of ticagrelor in CAS in this study.

Methods: The records of the patients who underwent CAS between January 2020 and January 2022 were scanned and the patients who were treated with the ASA and ticagrelor therapy were included in this study. Demographic data of the patients, vascular risk factors, ipsilateral-contralateral stenosis rates, balloon angioplasty application status, residual stenosis rates, periprocedural ischemic and hemorrhagic events, and vascular events developed during three-month follow-up were noted.

Results: Thirteen patients were included in the present study. Their mean age was 69.38±7.1 years. The mean carotid stenosis rate was 82.07±10.44%, and contralateral stenosis rate was 65.07±32.98%. Stent thrombosis was not observed in any patient. After the procedure, minor ischemic stroke that did not cause disability developed in one patient and puncture site bleeding that did not require transfusion in one patient. One patient had >50% restenosis at three months.

Conclusion: The findings suggest that dual antiplatelet therapy with ticagrelor + ASA appears to be a safe and effective treatment for CAS. Given that clopidogrel resistance cannot be evaluated in many centers, it may be more accurate to prefer ticagrelor, especially in high-risk patients with bilateral stenosis.

Keywords: Carotid artery, clopidogrel, stent, stroke, ticagrelor

ÖZ

Amaç: Karotis arter stentleme (KAS) sonrası trombotik komplikasyonları önlemek amacıyla asetilsalisilik asit (ASA) ve klopidogrel tedavisine en az bir ay devam edilmesi sonrasında tekli antiagregan kullanımı önerilmektedir. KAS'de tikagrelor kullanımı ile ilgili ise az sayıda çalışma bulunmaktadır. Bu çalışmada KAS'de ikili antiagregan tedavi olarak ASA ve tikagrelor kullanımının etkinliği ve güvenilirliğini değerlendirmeyi amaçladık.

Yöntem: Ocak 2020 ile Ocak 2022 tarihleri arasında kliniğimizde KAS uygulanmış olan hastaların dosyaları tarandı. ASA ve tikagrelor tedavisi altında stent uygulananlar çalışmaya alındı. Hastaların demografik verileri, vasküler risk faktörleri, ipsilateral-kontralateral darlık oranları, balon anjiyoplasti oranları, rezidü darlık oranları, periprosedürel ve postoperatif üç aylık takiplerinde gelişen olaylar kaydedildi.

Bulgular: Çalışmaya toplam 13 hasta alındı. Ortalama yaş 69,38±7,1 idi. Karotis arter darlık oranları ortalama %82,07±10,44 idi. Kontralateral darlık oranları ise %65,07±32,98 idi. Hastaların takiplerinde bir hastada transfüzyon gerektirmeyen ponksiyon yeri kanaması, bir hastada minör iskemik inme gelişti. Stent trombozu hiçbir hastada izlenmedi. Üçüncü ayda >%50 restenoz bir hastada saptandı.

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Corresponding Author:
A. Yabalak
ORCID: 0000-0002-3317-9567
Düzce University, Faculty of Medicine, Department of Neurology, Düzce, Türkiye
✉ yabalakahmet@gmail.com

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Sonuç: Ticagrelor ve ASA ikili antiagregan tedavisi karotis stentlemede güvenli ve etkin bir tedavi olarak görünmektedir. Klopidogrel direncinin ülkemizde birçok merkezde yapılamadığı da göz önüne alındığında özellikle yüksek riskli ve bilateral darlığı olan hastalarda ticagrelor başlamak doğru bir tercih olabilir.

Anahtar kelimeler: İnme, karotis arter, klopidogrel, stent, tikagrelor

INTRODUCTION

Carotid artery stenting (CAS) is an alternative treatment to endarterectomy for symptomatic and asymptomatic carotid artery stenosis. The frequency of minor ischemic stroke in CAS procedures is still higher than in endarterectomy despite all technical developments in current studies (1). It is recommended that CAS be performed under dual antiplatelet therapy (DAPT). The acetylsalicylic acid (ASA) + clopidogrel combination is frequently used in clinical practice (2). Clopidogrel is an irreversible inhibitor of P2Y12. Approximately 85% of clopidogrel absorbed from the intestines is converted into an inactive metabolite, while the remaining 15% is metabolized by cytochrome P450 enzymes in the liver to become active. Inter-individual variability in liver metabolism may result in decreased efficacy. Efficiency decreases, especially in genotypes carrying the CYP2C19 loss-of-function allele (3). Studies have reported that patients with cerebrovascular diseases have a decreased resistance or response to clopidogrel up to 66% (3,4). However, a study conducted in 26 countries has shown that platelet function tests can only be performed in 16% of centers (4). It is obvious that an effective antithrombotic treatment is required to prevent thrombotic complications that may develop after stenting, and an alternative treatment is needed because of the inadequate response to clopidogrel in approximately one-third of the patients (5).

Ticagrelor is a metabolite that noncompetitively and reversibly inhibits P2Y12 receptors. The most important difference from other P2Y12 antagonists is that it is an active drug and does not need to be metabolized. It has linear pharmacokinetics due to its high protein binding rate (6). The advantage of its pharmacokinetic property reduces individual differences in efficacy, and the antiplatelet activity begins rapidly. In case of any bleeding or side effects, the efficacy disappears quickly after the discontinuation of the drug (7). In studies, the probability of high platelet activity during the procedure was reported to be between 1.5% and 4% in those receiving ticagrelor (8,9). This rate is quite low compared to clopidogrel.

As data on the use of ticagrelor in cerebrovascular diseases increased, it has begun to be recommended in the guidelines. The AHA/ASA guideline recommends the use of ticagrelor in addition to aspirin for 30 days in patients with new minor ischemic stroke and high-risk transient ischemic attack (TIA) patients with >30% stenosis of major intracranial vessels as the level of evidence IIb (10). To our knowledge, there are no randomized controlled studies and recommendations for its use in CAS other than observational studies. In our country, ticagrelor is not reimbursed by the Social Security Institution in the neurology branch. Therefore, we wanted to evaluate the efficacy and safety of this treatment by sharing the data of patients who underwent CAS under ticagrelor + ASA dual antiplatelet therapy in this study.

MATERIALS AND METHODS

After obtaining the approval for the study from Bolu Abant İzzet Baysal University Ethics Committee (date: 03/01/2023, number: 2022-292), the data of patients who underwent CAS under ASA and ticagrelor antiplatelet therapy between January 2020 and January 2022 were evaluated. Patients' age, symptomatic or asymptomatic stenosis status, ipsilateral, contralateral and residual stenosis rates, periprocedural ischemic and hemorrhagic complications, and neurological and cardiac events developed in the three-month follow-up were recorded. It was noted whether silent ischemic lesions developed in patients with diffusion MRI control before and after the procedure.

Statistics

Data were analyzed using the SPSS 22.0 (IBM Corp.; Armonk, NY, USA) program. Categorical variables were expressed as numbers and percentages, and countable variables as means ±SD.

RESULTS

A total of 13 patients (eight male [61%] and five female [39%]) who underwent CAS under ticagrelor and ASA DAPT were included in the present study. The mean age of the patients was 69.38±7.1 (years) (range, 59-83). Vascular risk factors and demographic data of the patients are shown in Table 1. In addition, the demographic, radiological, and clinical data of the cases are given in Table 2 as a patient list. All patients underwent stenting for symptomatic stenosis. The right ICA was stented in six patients (46%) and the left ICA in seven patients (54%). An open-cell stent was used in five patients (39%), and a closed-cell stent was used in eight patients (61%). While distal filters were used in eight patients (61%), no embolic protection device was used in five (39%) patients. The mean ICA stenosis rates were (rate was) 82.07±10.44 (min-max 62-99). The mean contralateral ICA stenosis rate was 65.07±32.98 (10-100). Ten of 13 patients (76%) had more than 50% stenosis in the contralateral ICA. Of these 10 patients, three had contralateral ICA occlusion and two had preocclusive stenosis. None of the patients had residual stenosis greater than 30% after the procedure. A new silent ischemic lesion was detected in five (62%) of eight patients who had diffusion MRI examinations before and after the procedure. A minor ischemic stroke was observed in one patient with the clinic of mild right hemiparesis after the procedure. One patient developed puncture site bleeding that did not require transfusion. No major ischemic event or major hemorrhage was observed three months after the procedure.

DISCUSSION

In this case series, no major ischemic or hemorrhagic events were observed in 13 patients who were treated with CAS under ticagrelor and ASA DAPT and generally had bilateral stenosis. Ticagrelor has started to be used in coronary artery disease after the Dose conflrmation Study assessing antiPlatelets Effects of AZD6140 vs. clopidogRel in non–ST-segment Elevation myocardial infarction (DISPERSE-2) and the Platelet Inhibition and Patient Outcomes (PLATO) studies, which were first published in 2009. The PLATO study reported that almost all patients with clopidogrel resistance had adequate platelet inhibition (11,12).

The first large randomized, controlled study on its use in cerebrovascular diseases is the Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES), published in 2016 (13). In this study, which included high-risk TIA or minor ischemic stroke patients, ischemic stroke was reported to be lower in the ticagrelor group than in the ASA group during the 3-month follow-up. Death and

Table 1. Vascular risk factors, procedural and follow-up data of patients.

Age	69.38±7.13	**Symptomatic n(%)**	13 (100)
M/F n(%)	8(61.5) /5(38.5)	**Stenosis rate (%)**	82.3±10.44
DM n(%)	9(69.2)	**Contralateral stenosis rate (%)**	65.07±32.98
HT n(%)	10(76.9)	**Predilatation n(%)**	8 (61.6)
History of prior stroke n(%)	6 (46.2)	**Postdilatation n(%)**	9 (69.3)
Coronary artery disease n(%)	5 (38.5)	**Residual stenosis rate (%)**	15.3±11.18
Smoker n(%)	6 (46.2)	**Those who had DWI MRI after the procedure**	8/13
Hyperlipidemia n(%)	10 (76.9)	**New ischemic lesion (%)**	5/8 (62.5)
Events in the first 3 months of follow-up	Restenosis>50% 1/13	Puncture site bleeding 1/13	Minor stroke 1/13

M: Male, F: Female, HT: Hypertension, DM: Diabetes mellitus, DWI MRI: Diffusion-weighted magnetic resonance imaging

Table 2. Patient list and demographic and radiological data of patients.

Case	Age	Gender	Stenosis rate	DM	HT	HL	History of prior stroke	CAD	Contralateral stenosis rate	Predilatation	Postdilatation	Distal filter	Residual stenosis rate	Post-procedure DWI MRI control	New ischemic lesion
1	67	M	82	+	+	-	+	+	30	+	+	+	0	-	
2	83	F	95	+	+	+	+	-	53	+	-	-	10	-	
3	63	M	72	+	+	+	+	+	100	-	-	+	27	+	+
4	67	M	84	-	-	+	-	-	50	+	+	+	25	-	
5	65	M	88	+	-	+	-	-	99	+	+	+	23	-	
6	60	M	85	+	+	+	+	-	98	+	+	+	0	+	+
7	74	F	72	-	+	+	-	+	62	-	+	+	16	+	-
8	74	F	62	-	+	+	-	+	10	-	+	-	10	-	
9	74	F	94	+	-	-	+	-	66	+	+	-	28	+	+
10	65	F	99	+	+	+	-	-	15	+	+	-	24	+	+
11	59	M	75	+	+	+	-	-	100	+	-	+	28	+	-
12	75	M	83	-	+	-	+	-	63	-	+	-	8	+	+
13	76	M	79	+	+	+	-	+	100	-	-	+	0	+	-

M: Male, F: Female, HT: Hypertension, DM: Diabetes mellitus, HL: Hyperlipidemia, CAD: Coronary artery disease, DWI-MRI: Diffusion-weighted magnetic resonance imaging

myocardial infarction (MI) were observed less frequently in the ticagrelor group. In the subgroup analysis, it was reported that ticagrelor was more effective in preventing recurrent ischemic events than ASA in patients with ipsilateral large vessel atherosclerosis. There was no difference in the rates of major bleeding and intracranial bleeding between the two groups (13). In the Platelet Reactivity in Acute Nondisabling Cerebrovascular Events (PRINCE) study[14], patients who were administered ASA+clopidogrel and ASA+ticagrelor were compared to patients presenting with TIA or stroke; in the 3-month follow-up, stroke recurrence was less in the ASA+ticagrelor group, especially in those with large vessel atherosclerosis. The fact that only patients from rural China were included in the study prevented the generalizability of the study (15). Patients with mild to moderate acute noncardioembolic ischemic stroke (NIHSS score ≤5) or TIA who did not undergo intravenous or endovascular thrombolysis were enrolled in the Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES) study. They were randomized to treatment with ASA or ASA+ticagrelor. The total risk of stroke and death within 30 days and the risk of ischemic stroke alone were lower in the ASA+ticagrelor group. Although it did not reach statistical significance, major bleeding was more common in the ASA+ticagrelor group (16). When patients with ipsilateral stenosis were compared in the subgroup analysis of the THALES study, 30-day ischemic stroke and death were less in the ASA and ticagrelor group compared to the ASA group (8.1% vs. 10.9%) (17). In the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE II) study, 6412 patients with minor ischemic stroke and TIA with the CYP2C19 loss of function allele were randomized 1:1 to clopidogrel+ASA and ticagrelor+ASA treatments. In the 3-month follow-up, the risk of stroke was lower in the ticagrelor group, while dyspnea, arrhythmia, and total bleeding were more common. The main limitation of the study was that it could not be generalized because only Han patients were included in the study (18).

A meta-analysis study reported that the use of ticagrelor had a positive effect on primary and secondary stroke prophylaxis, and there was

a small increase in major and minor bleeding, although this was not statistically significant for major bleeding. It has been reported that dyspnea and hyperuricemia may develop as the most important factors limiting its utilization (19). As studies on its use in ischemic stroke have increased, the use of ticagrelor has started to be included in the guidelines (10).

To our knowledge, there is no large randomized controlled study on the use of ticagrelor in neuroendovascular treatment, but there are case series and cohort studies. Hanel et al.[5] reported that in 18 patients with clopidogrel resistance who underwent neuroendovascular treatment and were switched to ticagrelor treatment, there were no ticagrelor-related side effects or no worsening of clinical outcomes. In the study conducted by Qureshi et al.[20], it was reported that 70 of 106 patients undergoing neuroendovascular intervention had suboptimal platelet inhibition with ASA+clopidogrel treatment, and optimal platelet inhibition developed in 50 of these 70 patients with ticagrelor. Fifi et al.[21] reported that periprocedural thromboembolic complications were more common in patients with clopidogrel resistance in neurovascular stenting applications. In the study by Narata et al.[22], the data of 154 patients who underwent intracranial stenting under ticagrelor and ASA treatment for unruptured aneurysm closure, ticagrelor, and ASA were administered without platelet function testing in all patients, and the patients were followed up for three months after the procedure. In this study, they reported that ischemic complications were lower, and hemorrhage and death were similar to those in the literature in patients treated with both the flow-diverter stent and stent-assisted coils. The study by Karan et al.[23] reported that clopidogrel resistance was detected by a 25% optical light transmission platelet aggregometry (LTA) test in 32 of the patients who were scheduled for neuroendovascular intervention, and the procedure was performed after switching to ticagrelor treatment. None of these patients developed thromboembolic complications .

In the case series reported by Linfante et al.[24], in which patients who received iv (IV) cangrelor for subarachnoid hemorrhage and acute ischemic stroke followed by acute stenting and followed up with ticagrelor treatment, it was reported that this protocol could be an alternative regimen to clopidogrel in acute cases. While all patients who underwent neuroendovascular treatment were included in these studies, we specifically evaluated patients with CAS in our study.

In the study conducted by Kadoglou et al.[25] in rabbits with atherosclerotic carotid stenosis, it was reported that stent thrombosis was less common in rabbits under ASA and ticagrelor DAPT compared to the ASA and clopidogrel group. In the study conducted by Lotan et al.[26], clopidogrel resistance was detected in 110 (34%) of 325 patients who underwent CAS, and ticagrelor treatment was started. While there was no difference between the two groups in terms of cerebrovascular events, and minor and major bleeding, stent restenosis was significantly lower (9 vs. 0) in the ticagrelor group. In a retrospective study by Marcaccio et al.[27] comparing the patients who underwent CAS under ASA + clopidogrel and ASA + ticagrelor treatments, puncture site bleeding was reported to be higher in the ASA + ticagrelor group (5.9% vs. 3%) in patients with transfemoral access. It was reported that there was no difference between the two groups in terms of stroke and death. It was reported that no ischemic stroke, death, or intracranial hemorrhage developed in the 30-day follow-up of 18 patients who had clopidogrel resistance and underwent CAS under ticagrelor + ASA DAPT as reported by Olafson et al (28).

Ghamraoui et al.[8] evaluated 67 patients who underwent CAS with the transcarotid artery revascularization method under ASA+ticagrelor dual antiplatelet therapy and reported that none of the patients developed stroke, MI, or major bleeding during their 30-day follow-up. In this study, it was reported that 8% of the patients developed severe dyspnea and had to change their medication. In the three-month follow-up of

our cases, a minor ischemic stroke was observed in one patient, and bleeding at the puncture site was observed in one patient. The most significant distinguishing feature of our cases was the high prevalence of contralateral ICA stenosis. In 76% of the patients, there was more than 50% stenosis in the contralateral ICA.The most important side effect limiting the use of ticagrelor is dyspnea. Dyspnea due to ticagrelor has been reported in a range of 4.8-14% (8,29). Although it is usually temporary, it may progress and require discontinuation of the drug. Dyspnea was not observed in our cases.

The gold standard test for evaluating platelet inhibition due to P2Y12 inhibitors is the LTA test. Its use in daily practice is limited due to the difficulty of sample preparation, the need for experience and the time-consuming test results (3). More clinically convenient platelet function tests include the VerifyNow assay (Accumetrics, San Diego, Calif), Multiplate Analyzer (F. Hoffmann-La Roche Ltd, Basel, Switzerland), vasodilator-stimulated phosphoprotein phosphorylation assay (Diagnostica Stago, Biocytex, Asnières, France), and A thromboelastography-platelet mapping (TEG-PM). However, these tests cannot be performed in many centers. A multinational study reported that it could only be performed in 16% of the centers (4).

CONCLUSIONS

Ticagrelor and acetylsalicylic acid DAPT appears to be a safe and effective treatment for CAS. Given that clopidogrel resistance is not possible in many centers in Turkey, we think that ticagrelor should be preferred over clopidogrel, especially in high-risk patients with bilateral stenosis. There is a need for multicenter, control-group studies on this subject. The results of the ongoing Prevention of Cerebral Ischemia in Stent Treatment of Carotid Artery Stenosis A randomised multi-centre Phase II Trial, comparing ticagrelor versus clopidogrel with outcome assessment on MRI, (PRECISE-MRI) (ClinicalTrials.gov Identifier: NCT02677545) will also shed light on which antiplatelet therapy should be selected for CAS.

Ethics Committee Approval: The study protocol was approved by the Bolu Abant İzzet Baysal University Ethics Committee (03/01/2023 / 2022-292).

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