Comparison of Preoperative Single and Dual Antiplatelet Therapy in Bleeding After Carotid Endarterectomy

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ABSTRACT

Introduction: Single or dual antiplatelet therapy (SAPT or DAPT) is indicated in all patients with carotid artery stenosis (CAS), irrespective of clinical symptoms and revascularisation. In patients with carotid endarterectomy (CEA), SAPT or DAPT preoperatively may increase the risk of bleeding during surgery and postoperative period. There is no consensus regarding the discontinuation of preoperative treatment, especially in patients using clopidogrel. Our goal was to find the solution to this problem.

Patients and Methods: A total of 54 patients undergoing CEA were included in the study and evaluated retrospectively. Two different groups were formed: patients who used aspirin only in the preoperative treatment, containing SAPT (SAPT group, n= 34), and aspirin with clopidogrel, containing DAPT (DAPT group, n= 20). The patients were evaluated for perioperative bleeding, which needed re-exploration, drainage, revision due to haematoma, blood and blood-product change, or included other complications.

Results: Perioperative bleeding and drainage amounts were measured as 207.5 ± 90.4 cc in the DAPT group and 177.9 ± 93.9 cc in the SAPT group, and no significant difference was observed when the groups were compared (p= 0.263). One patient in the DAPT group was revised because of haemorrhage, and one patient in the SAPT group was re-operated due to haematoma (p= 0.699). No patients were found to have suffered myocardial infraction, cranial nerve damage, or death during hospital stay.

Conclusion: We recommend that clopidogrel in the prevention of cerebrovascular events in neurology should be primarily continued in the cardiovascular surgery without any interruption in patients with CEA.

Key Words: Carotid endarterectomy; clopidogrel; aspirin; bleeding

Karotid Endarterektomi Sonrası Kanamada Preoperatif Tekli ve İkili Antiplatelet Tedavinin Karşılaştırılması

ÖZET

Giriş: Tekli veya ikili antiplatelet tedavi (TAPT veya İAPT), klinik semptomlar ve revaskülarizasyondan bağımsız olarak karotis arter darlığı (KAD) bulunan tüm hastalarda endikedir. Karotis endarterektomi (KEA) uygulanacak hastalarda preoperatif TAPT veya İAPT, cerrahi sırasında ve postoperatif dönemde kanama riskini arttırabilir. Özellikle klopidogrel kullanan hastalarda preoperatif tedavinin kesilmesi konusunda fikir birliği yoktur. Bu sorunun çözümüne katkıda bulunmayı amaçladık.

Hastalar ve Yöntem: Çalışmaya KEA uygulanan 54 hasta alındı ve retrospektif olarak değerlendirildi. Ameliyat öncesinde sadece aspirin içeren TAPT (TAPT grubu, n= 34) ve klopidogrel ile aspirini içeren İAPT (İAPT grubu, n= 20) kullanmış hastalardan iki farklı grup oluşturuldu. Hastalar tekrar eksplorasyon gerektiren perioperatif kanama, drenaj, hematom nedeniyle revizyon, kan ve kan ürünü kullanımı ve diğer komplikasyonlar (miyokart infarktüsü, kraniyal sinir hasarı ve ölüm) açısından değerlendirildi.

Bulgular: Perioperatif kanama ve drenaj miktarları İAPT grubunda 207.5 ± 90.4 mL, TAPT grubunda 177.9 ± 93.9 mL olarak ölçüldü ve gruplar karşılaştırıldığında anlamlı fark gözlenmedi (p= 0.263). İAPT grubundaki bir hasta kanama nedeniyle revize edildi ve TAPT grubundaki bir hasta hematom nedeniyle tekrar ameliyat edildi (p= 0.699). Hiçbir hastada miyokart infarktüsü, kraniyal sinir hasarı ve hastanede kalış süresi boyunca ölüm saptanmadı.

Sonuç: Nörolojik tarafta serebrovasküler olayların önlenmesinde primer olarak kullanılan klopidogrelin, kardiyovasküler cerrahi alanında da KEA planlanan hastalarda operasyon öncesi kesinti yapılmadan devam ettirilmesini öneriyoruz.

Anahtar Kelimeler: Karotid endarterektomi; klopidogrel; aspirin; kanama

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INTRODUCTION

Dual antiplatelet therapy (DAPT) including an aspirin and clopidogrel combination is known to reduce major complication rates such as stroke and myocardial infarction (MI) in patients undergoing carotid endarterectomy (CEA)[1-3]. Recently, the combined use of those two agents for antiplatelet therapy has become more common, and this combination has been found to be more effective against thromboembolic complications in percutaneous coronary intervention as compared to the single antiplatelet therapy[4,5]. SAPT was recommended primarily for preoperative antithrombotic treatment in patients undergoing CEA, and clopidogrel addition was recommended in high-risk patients[6]. Despite those positive contributions, antiplatelet therapy may increase the morbidity and mortality in some surgical procedures. Particularly the combined use of aspirin and clopidogrel aggravate this negative side effect, which causes the problem of bleeding, especially in open-heart surgery[7]. Although this treatment has been reported as safe with regard to bleeding in patients with peripheral artery disease undergoing antiplatelet therapy, there is no consensus among vascular surgeons regarding the preoperative use of antiplatelets[8,9]. Nevertheless, considering the risk of MI, stroke and death in carotid surgery, bleeding and bleeding-related complications appear to be much more easily manageable problems. Particularly the anatomic location of the carotid artery and the small size of the surgical site allow easier intervention in possible bleeding. In this retrospective study, we aimed to evaluate the impact of aspirin with clopidogrel therapy on bleeding and bleeding-related complications in comparison to that of aspirin-only therapy by assessing the amount of perioperative drainage, revision due to haematoma and bleeding at the surgical site, blood and blood-product replacement, and other complications (MI, cranial nerve damage and death).

PATIENTS and METHODS

In the present study, 87 patients monitored by the department of neurology for symptomatic carotid stenosis and put on antiplatelet therapy for at least 1 month for cardiovascular reasons in the preoperative period, who subsequently underwent CEA, were evaluated retrospectively. A total of 54 patients complying with the study criteria were included in the study. The participants were categorised into two groups regarding the antiplatelet therapy they received in the preoperative period. The SAPT group (n= 34) received only aspirin (100-300 mg/day) in the preoperative period, while the DAPT group (n= 20) received a combination of aspirin (100-300 mg/day) and clopidogrel (75 mg/day). The medication used by patients (SAPT or DAPT) was the choice of physician, regardless of reason. The demographic profile and risk factors are presented in Table 1.

Inclusion Criteria

1. Symptomatic patients with carotid artery stenosis (CAS) ≥ 70%, documented by invasive imaging methods, who underwent CEA.

2. Patients who were on an aspirin-only or aspirin + clopidogrel combination therapy for at least 1 month until the time of the operation.

Exclusion Criteria

1. Patients who underwent combined surgery (CEA/CABG),

2. Patients with occlusion on the contralateral carotid artery,

3. Patients with chronic renal failure,

4. Patients who were not receiving aspirin-only or aspirin + clopidogrel combination therapy at least 30 days prior to the surgery.

All patients were operated under general anaesthesia by two different surgeons. The study surgeons were both experienced physicians performing over 30 CEA procedures per year.

Under general anaesthesia, a longitudinal incision was made from the anterior SCM to the sternoclavicular junction. The external and common carotid artery were found. They were returned with the vascular tape. 5000 IU heparin was delivered

Table 1. Demographic profile and risk factors

	DAPT group (n= 20)	SAPT group (n= 34)	p
Age	69.7 ± 8.1	69.9 ± 8.9	0.914
Gender (male, female) (%)	65-35	61.8-38.2	0.812
Hypertension (%)	37.2	38.7	0.562
Diabetes (%)	32.5	38.3	**0.036**
Peripheral arterial disease (%)	29.1	31.6	0.221

Table 2. Medical data and outcomes of the groups

	DAPT group (n= 20)	SAPT group (n= 34)	p
Perioperative bleeding and drainage (mL)	207.5 ± 90.4	177.9 ± 93.9	0.263
Neck haematoma and surgical treatment (n)	1	1	0.699
Blood or blood-product replacement (n)	0	0	-

DAPT: Dual antiplatelet therapy, SAPT: Single antiplatelet therapy.

intravenously. Vascular clamps were placed, and arteriotomy was made from the anterior of the proximal common carotid artery to the diseased segment of the internal carotid artery.

Endarterectomy was started from the common carotid artery until it reached the normal intima in the internal carotid artery. Arteriotomy was closed with the autogenous vein or synthetic patches using the 6/0 polypropylene suture. Heparin was not neutralised after the procedure. During the surgery, no patient was subjected to a shunt, and each patient received a vacuum drain. The two groups were monitored and compared in terms of postoperative drainage at the surgical site, and revision surgery due to haematoma or bleeding.

For our study, permission was obtained from the Ar-Ge Unit of the Ministry of Health Medicine and Medical Services from the local ethics committee numbered 65355327-604.01.02-E.134 by decision number 22.

Statistical Analysis

The Shapiro-Wilk test revealed a normal distribution for the continuous measures. The intergroup differences were assessed using Student's t-test, while the comparison of values before and after the operation was performed using the paired t-test. The mean and standard deviation values were used as the descriptive statistics. Pearson's chi-squared test was employed for the intergroup differences in categorical variables. A p-value < 0.05 was recognised as statistically significant.

RESULTS

There was no significant difference between the groups in terms of age (p= 0.914) and gender (p= 0.812). The diabetes mellitus rate was significantly higher in the DAPT group (p= 0.036). There was no statistically significant difference between the two groups in terms of peripheral arterial disease and hypertension. Demographic data and risk factors of patients are shown in Table 1. The mean postoperative drainage amounts were 207.5 ± 90.4 mL in the SAPT group and 177.9 ± 93.9 mL in the DAPT group, and there was no significant difference between the groups in this regard (p= 0.263). In the SAPT group, one patient underwent revision surgery due to bleeding, while one patient in the DAPT group had revision for haematoma (Table 2). During the hospital stay, none of the patients developed cranial nerve injury, MI, stroke, or died and no patients needed blood transfusion (Table 2).

DISCUSSION

In the present study, despite the 29.6 mL higher drainage value in the DAPT group, there was no significant difference between the SAPT and DAPT groups, and no patients required blood or a blood-related product replacement. Because the two groups did not reveal a significant difference regarding perioperative bleeding and drainage, our results suggest that SAPT can be safely continued in patients undergoing CEA.

Although the use of aspirin with clopidogrel in symptomatic patients with CAS is still contentious, it is recommended in acute coronary syndrome, for the prevention of recurrent ischaemic attacks after percutaneous coronary intervention, and to increase the graft patency after CABG[10]. Markus et al.[11] compared SAPT and DAPT groups in 107 symptomatic patients with a CAS ≥ 50%, and DAPT was found to be more effective in reducing the thromboembolic complication rates of transient ischaemic attack (TIA) and ischaemic stroke as compared to SAPT. On the other hand, Payne et al.[12] noted that DAPT reduced the rate of cerebral embolisation in CAS. On contrary, the MATCH study reported no difference between the DAPT and clopidogrel alone groups regarding the primary end points[13]. Although there is no consensus on whether DAPT is useful in cases of CAS, nearly all patients with CAS use SAPT or DAPT. The highest risk in these patients is thromboembolic neurological complications, followed by bleeding and bleeding-related complications associated with the antiplatelet therapy. During the preoperative period, the discontinuation of the antiplatelet therapy may lead to thromboembolic complications such as TIA and stroke. Çerşit et al.[14] reported short-term results after endovascular intervention to carotid artery and reported that success rates for the CAS, considered as an alternative to CEA, are closely related to pre-treatment. Therefore, in patients undergoing CEA, continuing the antiplatelet therapy during the preoperative period appears to be a good decision. However, there are

vascular surgeons who prefer to discontinue the antiplatelet therapy due to perioperative bleeding and bleeding-related complications. Jackson et al.[15] conducted a study including 235 vascular surgeons, and no consensus was reached on whether SAPT or DAPT therapies should be discontinued before CEA. The main reason behind the failure to reach a consensus is the lack of knowledge involving the pros and cons. Nonetheless, in one study, preoperative SAPT and DAPT patients who underwent CABG were evaluated with regard to life-threatening bleeding, and the DAPT group demonstrated a 1.3-fold higher rate than that of the SAPT group; however, the stroke, MI and cardiovascular mortality rate was 44% lower in the DAPT group[16]. In the study in which Barracchini et al.[17] reported patients with 1458 CEA, the use of clopidogrel, clopidogrel + aspirin combination and ticlopidine when continued the day before the operation was associated with neck bleeding requiring postoperative re-exploration, whereas no neck bleeding was associated with preoperative treatment with dipyridamole and warfarin or no medication. As shown by the literature, even in the same study, patients on antiplatelet therapy may exhibit contradictory results regarding bleeding-related complications associated with surgery.

In patients with DAPT, performing major operations such as open-heart surgery may lead to reasonable doubts about possible bleeding and bleeding-related complications because of the large surgical site and a high number of involved surgical procedures. It is recommended to discontinue clopidogrel 5 days before the operation in patients undergoing CABG[18]. However, applying an attentive surgical approach, using a biological patch, performing heparin reversal, using an absorbable haemostat and placing negative-pressure drains may minimise a possible bleeding during the perioperative and postoperative periods in patients undergoing CEA. Gisbert et al.[19] found no significant difference in bleeding-related reoperation rates with regard to anaesthesia method (local or general), surgical technique (classic endarterectomy or eversion technique), patch type (dacron or PTFE), shunt use and heparin reversal; however, Mazzalai et al.[20] reported that heparin reversal reduced bleeding risk in the early postoperative period, but did not increase the risk of ischaemic cerebral events.

STUDY LIMITATIONS

This study has several limitations. First, data were retrospectively collected. Second, the number of patients in our study may seem relatively small compared to previous studies. Third, the INR values, platelet counts, aPTT and bleeding time were not included in the study, so we were unable to associate these values with bleeding and haematoma during the perioperative period.

CONCLUSION

Cardiovascular surgeons may prefer to discontinue DAPT before surgery to decrease the risk of perioperative bleeding, but they can continue DAPT to prevent perioperative neurologic events in some cases. Data that support both approaches are limited, and they are mainly in favour of discontinuing treatment related to literature on cardiovascular procedures.

We believe that by taking these precautions, bleeding and bleeding-related complications can be minimised and made much more tolerable. Thus, we recommend continuing DAPT during the preoperative period.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ÖV
Analysis/Interpretation: ÖV
Data Acquisition: ET
Writting: ÖV, ET
Critical Revision: ÖV, ET
Final Approval: ÖV, ET

REFERENCES

1. Nicolaides AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, Thomas DJ, et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratifi cation. J Vasc Surg 2010;52:1486-96.
2. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. AHA Guideline: Effectiveness-based Guidelines for the Prevention of Cardiovascular Disease in Women 2011 Update. Circulation 2011;23:1243-62.
3. Engelter S, Lyrer P. Antiplatelet therapy for preventing stroke and other vascular events aft er carotid endarterectomy. Stroke 2004;35:1227-8.
4. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.
5. Steinhubl SR, Berger PB, Mann JT, Fry ET, De Lago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-20.
6. Paciaroni M, Bogousslavsky J. Antithrombotic therapy in carotid artery stenosis: an update. Eur Neurol 2015;73:51-6.
7. Miceli A, Duggan SM, Aresu G, de Siena PM, Romeo F, Glauber M, et al. Combined clopidogrel and aspirin treatment up to surgery increases the risk of postoperative myocardial infarction, blood loss and reoperation for bleeding in patients undergoing coronary artery bypass grafting. Eur J Cardiothorac Surg 2013;43:722-8.
8. Schoenefeld E, Donas KP, Radicke A, Osada N, Austermann M, Torsello G. Preoperative use of aspirin for patients undergoing carotid endarterectomy. Vasa 2012;41:282-7.
9. Stone DH, Goodney PP, Schanzer A, Nolan BW, Adams JE, Powell RJ, et al. Clopidogrel is not associated with major bleeding complications during peripheral arterial surgery. J Vasc Surg 2011;54:779-84.

10. Fares RR, Lansing LS, Gallati CA, Mousa SA. Antiplatelet therapy with clopidogrel and aspirin in vascular diseases: clinical evidence for and against the combination. Expert Opin Pharmacother 2008;9:377-86.
11. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) trial. Circulation 2005;111:2233-40.
12. Payne DA, Jones CI, Hayes PD, Thompson MM, London NJ, Bell PR, et al. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. Circulation 2004;109:1476-81.
13. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. Lancet 2004;364:331-7.
14. Çerşit S, Şahin M. Karotis artere stent yerleştirme işleminde tersiyer merkez deneyimi ve kısa dönem sonuçlar. Koşuyolu Heart J 2018;21:93-7.
15. Jackson AJ, Teenan RP, Orr DJ. The use of clopidogrel in carotid endarterectomy: an audit of current practise. Eur J Vasc Endovasc Surg 2007;34:312-3.
16. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al. Clopidogrel in unstable angina to prevent recurrent ischaemic events trial. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-STelevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (CURE) Trial. Circulation 2004;110:1202-8.
17. Baracchini C, Gruppo M, Mazzalai F, Lorenzetti R, Meneghetti G, Ballotta E. Predictors of neck bleeding after eversion carotid endarterectomy. J Vacs Surg 2011;54:699-705.
18. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2610-42.
19. Gisbert SMM, Almonacil VAS, Garcia JMZ, Gascó BC, Palonés FJG, Monzón EO. Predictors of cervical bleeding after carotid endarterectomy. Ann Vasc Surg 2014;28:366-74.
20. Mazzalai F, Piatto G, Toniato A, Lorenzetti R, Baracchini C, Ballotta E. Using protamine can significantly reduce the incidence, of bleeding complications after carotid endarterectomy without increasing the risk of ischemic cerebral events. World J Surg 2014;38:1227-32.