Clopidogrel Loading or Maintenance Before Carotid Endarterectomy is Not Risky for Post-operative Bleeding or Wound Revision

Karotis Endarterektomi Öncesi Klopidogrel Yüklemesi veya Devamlı Kullanımı Postoperatif Kanama ve Yara Revizyonu İçin Riskli Değildir

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ABSTRACT Objective: To investigate whether clopidogrel loading or maintenance before carotid endarterec-tomy affecs postoperative bleeding or wound revision. **Material and Methods:** Patients with symptomatic carotid arterial disease were divided into 3 groups: group I was not on antithrombotic therapy, group II was on clopidogrel and antithrombotic therapy for at least 7 days, and group III was on antithrombotic therapy without clopidogrel and administered 600 mg clopidogrel 2 h before surgery. **Results:** Hemoglobin decreased in all groups. The differences between preoperative and postopera-tive values were statistically significant. Hematoma developed in a total of 4 patients; 2 of them were in group II, and 2 were in group III. No difference was found among the groups in terms of bleeding-related complications. **Conclusion:** Insignificant hemorrhage-related complications support administration of a loading dose of clopidogrel together with the ongoing anticoagulant-antiaggregant therapy before carotid endarterectomy.

Key Words: Endarterectomy, carotid; clopidogrel; hematoma; hemorrhage

ÖZET Amaç: Karotis endarterektomi öncesi klopidogrel yüklenmesi veya devamlı kullanımının postoperatif kanama ve yara revizyonuna etkisini araştırmak. **Gereç ve Yöntemler:** Semptomatik karotis arter hastaları 3 gruba ayrılmıştır. Grup I antitrombotik tedavi almayanlar, grup II en az 7 gündür antitrombotik ve klopidogrel alan hastalar, grup III ise klopidogrel olmaksızın antitrombotik tedavi almasına karşın, cerrahiden 2 saat önce 600 mg klopi-dogrel alan hastalardan oluşmaktadır. **Bulgular:** Tüm gruplarda hemoglobin değerleri düşmüştür. Preoperatif değerlere göre bu anlamlıdır. Grup II de 2, grup III'te 2 hastada olmak üzere, 4 hastada hematom gelişmiştir. Gruplar arasında kanama ile ilgili komplikasyonlar açısından bir fark bulunamamıştır. **Sonuç:** Kanama ile ilgili komplikasyonlar arasında bir fark olmaması, karotis endaterektomi öncesi antikoagülan ve antiagregan tedavisi devam eden hastalarda klopidogrel yüklenmesini desteklemektedir.

Anahtar Kelimeler: Endarterektomi, karotis; klopidogrel; hematom; kanama

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Endarterectomy is one of the main treatment methods in carotid artery stenosis.[1,2] Antithrombotic therapy (ATT) administered to patients during carotid endarectomy (CEA) and during complications early after CEA, at the time of surgery, during re-operations due to bleeding and hematomas may cause prolongation of hospital stay.[3-5] A study conducted among 650 vascular surgeons in Europe reported that clopidogrel administration was ceased 7 days before CEA.[6] Vascular surgeons in United Kingdom also act similarly, and 52% of them stop clopidogrel therapy before

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surgery. Forty nine percent of the surgeons that withdraw clopidogrel replace ATT with acetyl salisilic acid (ASA), whereas the remaining 51% do not administer ATT at all. Half of the 48% that prefers combination of ASA and clopidogrel carries on with only ASA therapy, while the remaining surgeons do not change their original recipe. Moreover, experienced surgeons that perform at least 30 or more CEA operations/year take place among the ones that cancels clopidogrel therapy postoperatively.[7] As it can be seen, there is no consensus among surgeons in terms of ATT protocols. The most important factor for this is bleeding and complications that may emerge due to bleeding when clopidogrel is used either on its own or in combination. This opinion is widely accepted for open heart surgical procedures; however outcomes of CEA operations performed when the patients are on clopidogrel are different from the results open heart surgery.[8-10]

The ATT that was applied worldwide included antiaggregants and/or anticoagulants, and it was usually used to prevent cardiovascular and cerebral mortality and morbidity. Therefore it has become a routine to administer 300-600 mg of clopidogrel to the patients just before undergoing percutaneous coronary intervention (PCI) or carotid stenting. The incidence of death due to myocardial and cerebral damage and the frequency of complications such myocardial infarction (MI) and stroke decreased with the use of this clopidogrel regime, however the complications related to bleeding in the insertion sites did not increase.[11-16] We investigated the effect of different ATT protocols; no ATT, ATT with clopidogrel, and ATT without clopidogrel and administration of 600 mg oral loading dose 2 h before CEA; in patients who underwent CEA in terms of development of bleeding/ hematoma.

MATERIAL AND METHODS

This study has been approved by Ethics Committee of T.C. Mersin University based on the decision statement no: 307.

The data of 57 patients who admitted or were referred to our department between 2010-2012, had 70% or more carotid artery stenosis on ultrasound in presence of clinical symptoms (the neurological symptoms were directly associated with stenotic carotid arteries), and underwent CEA were analyzed retrospectively. The patients who underwent concomitant coronary artery bypass grafting (CABG), had total occlusion on the contralateral carotid artery, and with deteriorated liver and/or kidney functions were excluded, and 51 patients were enrolled for assessment. Patients were divided into 3 groups focusing particularly on administration of clopidogrel:

- Group I (n=7): Patients that were not on any ATT preoperatively (p.o.),
- Group II (n=19): patients who were on clopidogrel and ATT therapy for at least 7 days, and
- Group III (n=25): patients with ongoing ATT without the inclusion of clopidogrel, and were administered 600 mg of clopidogrel p.o. 2 h before surgery.

The patients in all groups continued to receive 75 mg/d of clopidogrel following the CEA operations. Death, stroke, transient ischemic attack (TIA), MI, neck bleeding/hematoma during the first postoperative 24 h were analyzed. Moreover, preoperative and postoperative hemoglobin (Hb) levels, duration of surgery, re-operations and length of hospital stay were also analyzed.

All surgical procedures were carried out under general anesthesia. Heparin 100 IU/kg i.v. was given to each patient before a cross clamp was placed on the arteries. Application of a carotid shunt was decided according to the stump pressure peroperatively. The arteriotomy performed on the carotid arteries was closed using a patch of bovine pericardium, sutured with 6/0 polypropilene sutures. Heparin was not neutralized with protamine sulfate following the operations and no hemostatic materials like surgicel were used in any of the patients. All wounds were closed by placing single sutures to the fascia, subcutaneous tissue and the skin, after the placing a vacuum drainer following careful hemostasis. Patients were extubated after the closure of the wounds, and they were transferred to our intensive care unit (ICU) for early follow up

that lasted 3 h postoperatively where they were examined by a neurologist. Those that were neurologically and hemodynamically stable by the end of this period were transferred to the ward. The drains were usually removed 24 h after surgery in patients whose drainage were below 25 ml, or in whom the drained material gained a serous character.

STATISTICAL ANALYSIS

Shapiro Wilk test was used to test normal distribution of the variables, and it was determined that only age showed a normal distribution. One Way ANOVA was performed for normally distributed variables, and descriptive statistics were shown as mean ± standard deviation (SD). Kruskal-Wallis test was used for variables that were not normally distributed, and descriptive statistics were given as median and 25-75% quartiles. Differences between categorical variables were analyzed with Chi-square test, and the data were presented as numbers and percentages. Statistical analysis was performed with SPSS 11.5 (SPSS Inc. Chicago, Illionis). P values <0.05 were considered as statistically significant.

RESULTS

Patients demographics and analysis of all considered variables were given Table 1. The mean age of our patients was 68.39±8.86 years, and 70.6% of them were males. Hospital stay was 1.42±0.78 days in Group I, 3.00 ±2.86 days in Group II, and 1.96 ±1.74 days in Group III. There were no deaths, stroke, MI or TIA in any of the patients. The hospital stay was longer in Group II compared to other groups, as one patient was re-operated in this group due to hematoma, and another patient underwent tracheotomy due to dyspnea resulting from the pressure of hematoma on the trachea. However, there was no significant difference among the groups in terms of hospital stay (p=0.25).

In Group III, 2 patients underwent re-operation due to bleeding/hematoma, but there were no such complications in group I. When the groups were compared in terms of re-operations due to bleeding/hematoma, the difference among the groups was not statistically significant (p=0.68).

The preoperative and postoperative Hb values of the patients were also assessed as an indicator for bleeding. Preoperative mean Hb values in Groups I, II and III were 13.21±1.96, 12.59±2.3 and 12.72±1.83 g/dl while postoperative values were 11.58±1.54, 10.65±2.51, and 10.71±2.16 g/dl (p<0.001 for all) respectively. Despite statistically significant fall in Hb levels in all groups, the patients did not suffer from any hemodynamic instability. Preoperative and postoperative Hb levels of three groups were not significant (preoperative p=0.83, and postoperative p=0.65).

Duration of surgery was 60.71±4.49 min in Group I, 57.63±5.61 min in Group II, and 57.6±6.31 min in Group III. There was no statistical difference among the groups in terms of duration of surgery (p=0.45).

DISCUSSION

ATT composed of antiaggregants and/or anticoagulants is commonly used worldwide to prevent cardiac and cerebrovascular mortality and morbidity.[11,12] ASA and clopidogrel combination is particularly preferred for its superior benefits for

TABLE 1: Patients demographics and analysis of all considered variables.

	Group I	Group II	Group III	P value
n	7	19	25	
Age (mean ± SD)	71.0±8.8	65.2±7.9	70.1±9.2	0.129
Reoperation for hematoma/bleeding	0	2 (%10.52)	2 (%8)	0.68
Preop Hb (g/dl) (median [Quartiles])	13.6 [11.9-13.6]	12.4 [10.8-12.4]	12.8 [11.7-12.8]	0.833
Postop Hb (g/dl) (median [Quartiles])	11.1 [10.4-11.1]	11.4 [7.7-11.4]	11.0 [9.5-11.0]	0.659
Duration of operation (minute) (median[Quartiles])	60 [55-60]	60 [55-60]	60 [55-60]	0.450
Hospital Stay (day) (median [Quartiles])	1 [1-1]	2 [1-2]	1 [1-1]	0.252

TIA: Transient ischemic attack; MI: Myocardial infarction; Preop Hb: Hemoglobin levels before the operation; Postop Hb: Hemoglobin levels after the operation.

coronary and carotid artery diseases.[13,14] It has been put forward that a loading dose before percutaneous interventions enhances the effectiveness of ATT. It was suggested that thrombocyte aggregation decreased with the increased ADP activation in patients who were given 300-600 mg clopidogrel as a loading dose before PCI or carotid stenting, in relation with the given dose and time. Besides obtaining fewer complications such as death due to myocardial/cerebral damage, MI and stroke, the rate of complications and bleeding at the insertion sites did not increase.[15,16] The antiaggregant effect of clopidogrel was shown to be highest in patients who had been on clopidogrel 75 mg/day for at least 7 days, or in patients that were administered a loading dose of 600 mg p.o. 2 h before the intervention, and this effect was suggested to be even higher in patients who were on another antiaggregant therapy.[17-19] Taking those data into consideration, we allocated the patients who were on clopidogrel therapy in combination with another ATT for at least 7 days into Group II, and the patients who were on ATT without clopidogrel and were administered 600 mg loading dose p.o. 2 h before the operation were allocated to Group III. Although positive effects of clopidogrel and its combinations have been acknowledged in percutaneous interventions, surgeons hesitated to use clopidogrel in the preoperative period particularly in coronary artery bypass grafting operations as well as endoscopic and other surgical interventions due to risk of bleeding and related complications.[20-23] This is also the case for CEA.[5] Antiaggregants are widely used in the presence of carotid arterial disease. A multicenter study conducted in the United Kingdom reported that rate of prescription for antiaggregant therapies was approximately 70% in the presence of other peripheral arterial diseases, while this rate increased to 90% in carotid arterial diseases. The majority of the CEA patients are on ASA therapy while those administered both ASA and clopidogrel combination constitute 15%, a rate much higher when compared to patients with other peripheral arterial diseases.[24] Forty nine percent of our CEA patients received ASA while 37% were on both ASA and clopidogrel therapy, and this rate was higher when compared to some smaller studies.[25-27] This may be related due to cautious approach of the authors to use clopidogrel. The vascular study group in The United Kingdom also agree with use of clopidogrel and its combinations.[24]

None of our 51 patients faced with major complications like death, stroke, MI or carotid thrombosis during their hospital stays. It should be noted that 7 (13.7%) patients were in Group I, and did not receive ATT preoperatively. Combination therapy with clopidogrel was given to the remaining 44 patients; they either received it preoperatively, or were administered a p.o. loading dose 2 h before CEA. Our results support the findings of other studies in terms of favorable effects on cerebrovascular and cardiovascular events. However, absence of major complications in Group I patients may be attributed to small number of patients in this group, the surgical technique used, and early commencement of clopidogrel following CEA. Nevertheless, besides this positive effect of clopidogrel, bleeding and hematoma formation are among the most unwanted complications of CEA. Bleeding that requires re-operation is approximately 1-3%, and hematoma formation that necessitates treatment is approximately 5%.[28] Bleeding may deteriorate hemodynamic parameters while hematoma formation can threaten life by applying pressure on the trachea and the great vessels. It was reported that relieving such a complication with a re-operation increased the chance of stroke or nonfatal stroke and death 3-4 fold.[29]

Baracchini et al. reported neck bleeding/hematoma as 8.2% in their series of 1458 CEA, and 4.7% of them necessitated re-operation. In that series, 31.3% of the patients needed antihypertensive medication during bleeding. It was also reported that a 1.8 times and 2.6 times more bleeding was observed in patients that received clopidogrel and warfarin, respectively, when compared to the patients that received ASA alone. Those complications were more significant in hypertensive patients who were on clopidogrel and/or ASA therapy until the time of CEA. Half of the bleedings were stopped with conservative methods. However, stroke rate was 0.05% despite no deaths were

encountered. The patients who experienced major and minor stroke stopped antiaggregant therapies 5-6 days prior to surgery.[5]

In a multicenter retrospective study on 1488 patients, Hale et al. reported that bleeding was evident in 4.4% of the patients on clopidogrel and ASA treatment, while this rate was 0.9% in patients on ASA alone, and 1.2% in the ones that did not have any antiaggregant therapy. Bleeding was found to be 5.5 times more in patients that received clopidogrel and ASA, and reoperation rate for bleeding was 2.5%. It was concluded that administration of antiaggregants was not beneficial in terms of stroke, MI, cardiac arrest and death during the first 30 days, when patients using ASA and clopidogrel were compared to the patients who did not receive any antiaggregant therapy. Mortality was found to drop to 0.32% from 0.93%, TIA to 1.27% from 2.51% and MI to 0.00% from 0.39%. Hospital stays were also shorter in concordance with thoe findings.[30] Payne et al. reported that hypertension affected bleeding more than the antiaggregant therapy while Rosenboum blamed dacron graft which was used in the patch-plasty of the arteriotomies.[31,32] In a study conducted by Self et al. on patients that were not administred clopidogrel, hematoma formation was found in 12% of the patinets. The authors reported that use of ASA, shunt placement, preoperative hypotension and reversal of heparin were the factors affecting this result.[33] Checkik et al. reported that the use of clopidogrel did not have any adverse effects on bleeding, but it rather lengthened the time of the surgical procedure up to 330 m (205±52).[25] Rosenboum suggested that the duration of the operation in the control group was around 92 minutes while it lasted for 107 minutes in the clopidogrel-treated group. The difference was found to be significant.[32]

The duration of surgery was between 51.29 and 65.20 min when all 3 groups were taken into consideration. It suppose that the relatively short operation time is due to the use of bovine pericardium for the patch plasty, not using a shunt, and the accomplishment of the surgical procedures by a single surgeon.

When each group was analyzed separetely, we noticed a significant decrease in the postoperative hemoglobin compared to preoperative values, however this decrease did not give rise to hemodynamic alterations. Two patients in Group II needed re-operation; one for hematoma and the other for respiratory deterioration due to the pressure of hematoma to trachea needing tracheotomy. We acknowledge that tracheotomy could have been avoided by an earlier intervention to hematoma. Two patients in Group III received fibrinolytic therapy besides ASA and/or anticoagulant regime 1 week before CEA, and their neurological symptoms had been healed at the time of surgery. Two patients in this group that were administered clopidogrel loading dose, and 2 patients who received fibrinolytic therapy developed hematomas. Absence of bleeding-related complications in Group I, but development of hematoma in Groups II and III may be associated with administration of ATT and clopidogrel. On the other hand, the difference among the groups in terms of complications were found to be insignificant since the patients who developed hematomas have led to a minimal prolongation of hospital stay. Wait et al. also reported that bleeding/hematoma formation in the clopidogrel group lengthened hospital stay.[27] In this study, the rate of intervention for bleeding/hematoma formation was 7.84%, but when the groups were analyzed separately this rate was 10.52% in Group II, and 8% in Group III. Although only 2 patients in Group II, and 2 patients in Group III developed hematomas, the high re-intervention rates we found are due to small number of patients included in each group. In literature, some studies reported high major and minor complications rates due to small number of patients included.[25-27] Stone et al. indicated that rate of bleeding that required re-operation due to clopidogrel use was 0.05% in 5264 CEA patients while bleeding due to clopidogrel and ASA combination was 1.5% and this rate was similar to the rate found in patients that did not use any antiaggregant therapy. However, bleeding due to use of ASA alone was 1.3%.[24]

The majority of the studies that investigated CEA on patients receiving antiaggregant therapy

have commonly referred to the lower ratios of the major complications like death, stroke and MI, but somehow increased ratios of bleeding/hematoma formation. The highest rate for the latter complication was reported by Self et al. as 12%. In their study, many factors have been blamed for bleeding/hematoma development besides ASA use 33. The following high rate was reported as 8.2% where half of the patients necessitated re-operations. As 1/3 of those patients were hypertensive, hypertension was blamed as well as clopidogrel to be responsible for bleeding/hematoma formation5. On the other hand, in a study that blamed the only antiaggregants for being responsible for reported the re-operation rate due to bleeding as 1.5%, even in case of combined use of ASA and clopidogrel.[24]

In our opinion, the risk of bleeding and hematoma formation should be undertaken in an effort to reduce the major complications that can be seen at a rate of 5% after CEA. Prevention is dependent on the experience of the surgeon, meticulous operative technique, and hemostasis. We use cautery for dissection down to the level of the carotid sheath, and liberally use ligature for dissections after that point. Patches of bovine pericardium reduce the incidence of needle hole and suture line bleeding. Placement of a vacuum drain and use of single sutures for the fascia, subcutanous tissue and the skin seem to have favorable impact on desired results.

In conclusion, high bleeding/hematoma rates in our series are due to small numbers of subjects in the groups. Insignificant differences among the groups and absence of major complications such death, stroke and MI indicate that clopidogrel may reliably be used in the ATT protocols before CEA, or as a loading dose of 600 mg p.o. 2 h before CEA.

Conflict of Interest

Authors declared no conflict of interest or financial support.

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