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REVIEW **DERLEME**

DUAL ANTIPLATELET THERAPY IN ISCHEMIC STROKE

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ABSTRACT

Antiplatelet drugs are widely used for secondary prophylaxis of ischemic stroke. Antiplatelet therapy can significantly reduce the risk of vascular events among high-risk patients. This review highlights the improvements of the use of dual antiplatelet therapy, particularly aspirin and clopidogrel combination, for the prevention of non-cardioembolic ischemic stroke.
Key Words: Ischemic stroke, dual antiplatelet, therapy.

İSKEMİK İNMEDE İKİLİ ANTİAGREGAN TEDAVİ

ÖZET

Antiagregan ilaçlar iskemik inmenin sekonder proflaksisinde yaygın olarak kullanılırlar. Antiagregan tedavi yüksek riskli hastalarda vasküler bir olay gelişme riskini anlamlı ölçüde azaltabilir. Bu derlemede kardiyoembolik olmayan iskemik inmenin önlenmesinde ikili antiagregan tedavi, özellikle aspirin ve klopidogrel kombinasyonunun kullanımı ile ilgili gelişmeler vurgulanmaktadır.
Anahtar Sözcükler: İskemik inme, ikili antiagregan, tedavi.

INTRODUCTION

Treatment options for secondary prevention in ischemic stroke can be listed as therapies for modifiable risk factors such as hypertension, diabetes, hypercholesterolemia, obesity, smoking, alcohol, physical inactivity, antiaggregant therapies such as aspirin, dipyridamole, ticlopidine, clopidogrel, ticagrelor, anticoagulant treatments such as warfarin, dabigatran, rivaroxaban, apixaban or heparin and vascular treatment (carotid endarterectomy and carotid angioplasty/stent). In this study, the drugs commonly used for secondary protection starting from acute period and in particular dual antiaggregant treatments in the light of new developments will be reviewed.

Numerous studies were made regarding whether or not an antiaggregant or anticoagulant treatment should be initiated in acute period for the patients who applied with an ischemic stroke, despite unknown etiologic diagnosis, and antiaggregant and anticoagulant drugs were compared with each other. IST (International Stroke Trial) is one of the most directive out of these studies in terms of their outcomes. Different doses of subcutaneous heparin and aspirin were administered randomly to 19435 patients with acute ischemic stroke, either separately or in combination. The outcomes of the study can be summarized as follows; The mortality rate in the first 14 days with heparin was lower than in those without heparin, but it was not significant and the 6-month results were found same. The recurrence of stroke in the first 14 days with heparin is less pronounced, however the hemorrhagic stroke increases, this is more apparent at doses above subcutaneous 5000 units twice per day. With Aspirin (Asa), the mortality and dependency is lower in 14 days and this trend continues in the 6-month results.

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The recurrence of stroke is lower in 14 days with Asa and no significant increase is observed in hemorrhagic stroke. The use in combination with low dose heparin and Asa can be better than use of single Asa, however the number of patients is not adequate in this study to show that. Further randomized studies with minimum 20000 patients are needed to clarify such results (1). IST results were found to support the initiation of Asa as early as possible in patients who admit with ischemic stroke.

There are 24 studies (23748 patients) with anticoagulant drugs (standard heparin, low molecular weight heparin, heparinoid) in patients with ischemic stroke within acute period. The evaluations of these studies are partially different from each other. When the results from especially 11 studies (22776 patients) are examined, there is no finding on that the initiation of anticoagulant therapy in first 14 days reduces the mortality rate; and similarly, no decrease is observed in mortality and dependence rates with early anticoagulant therapy. Anticoagulant therapy reduces the recurrence of ischemic stroke, but increases symptomatic intracranial hemorrhage. Symptomatic pulmonary embolism decreases, but the increase in extracranial hemorrhage is greater than this benefit (2).

On the other hand, when using antiaggregant drug in acute period (8 studies, 41483 patients), the results can be summarized as follows; When Asa therapy is initiated within the first 48 hours, 13 out of every 1000 patients had a significant reduction in mortality and dependence rates, 7 fewer recurrent strokes and 1 less pulmonary embolism. On the other hand, 2 more intracranial hemorrhage occurred. According to these findings, the benefits are predominant with antiaggregant treatment, hemorrhage is lower and the antiaggregant treatment is recommended in the early period (3).

Acute period studies were mainly conducted with Asa. The CAST (the Chinese Acute Stroke Trial) study which was conducted by administering Asa 160 mg/day or placebo for 4 weeks to 20000 patients with ischemic stroke who admitted in the first 48 hours is the most comprehensive study ever conducted in this field, and in this study, Asa showed a significant decrease in stroke recurrence, a slight increase in bleeding risk, and a significant decrease in mortality and dependence rates (4). The results of meta-analysis regarding antiaggregant therapy in the acute period also support the use of Asa when there is no contraindication in patients. It is appropriate for all patients who admit with transient ischemic attack (TIA) or ischemic stroke to receive at least 160 mg of Asa. It should be delayed 24 hours for the patients who received thrombolytic therapy only (3,5).

Ischemic stroke recurs more frequently than hemorrhagic cerebrovascular disease. Although recurrence rates vary according to etiology, the annual rate is around 10-20 %. Recurrent strokes constitute at least 25-30 % of patients who admit to stroke clinics. Fatal progression is more frequent in repetitive strokes than in the first stroke (22 % vs. 41 %), causing more disability and higher costs. Therefore, all measures to prevent recurrence of stroke should be taken starting from the acute period.

Today, the mechanism of action of antiaggregant drugs is well known. Drugs in this group bind to different receptors on platelets, participate in different enzyme inhibitions, and block the adhesion, aggregation or secretion functions of the platelet. However, while these functions of platelets are affected, the hemostasis should not be impaired. Otherwise, complications of hemorrhage incompatible with life will occur. Today, the use of GP IIb/IIIa receptor blockers in stroke patients are not found appropriate because of the high rate of cerebrovascular bleeding complications. Ticlopidine is used very limited as it causes agranulocytosis. High percentages cannot be achieved always to prevent vascular events by an antiaggregant therapy to extent not to impair hemostasis. The results of 287 studies investigating the effect of antiaggregant treatment on vascular events are as follows; 7707 (10.7 %) vascular events (stroke, myocardial infarction (MI), vascular death) that occurred when 71912 patients took Asa, versus 9503 (13.2 %) vascular events occurred when 72139 patients took placebo (6). Relative risk reduction is significant, however not at a very high rate. Daily use of 30-300 mg Asa prevents only 13-22 % of vascular events (7). In acute period and chronic use, a serious vascular event with antiaggregant treatment alone decreases by 1/4, non-fatal myocardial infarction by 1/3, non-fatal stroke by 1/4, and vascular death by 1/6 (8). It should be

known that antiaggregant drugs may be insufficient to prevent a new vascular event and treatment of risk factors in stroke patients should be planned. The patient with stroke and his relatives should be informed about the expectation from the antiaggregant drug, and they should be told about the treatments regarding risk factors in particular and the importance of changes in lifestyle.

Antiaggregant drugs, aspirin, dipyridamole, thienopyridines (ticlopidine and clopidogrel) are widely used in patients with stroke, atherothrombotic stroke, small vessel disease (lacunar strokes) and stroke with no detectable etiology. Anticoagulant therapy is the first choice for patients with stroke who have been shown to be cardioembolic. Asa is the most widely used antiaggregant medication. It is commonly used in patients who have no gastric problems. For patients who underwent stroke despite the Asa or who cannot use Asa, other drugs will be referred. The drug selection criteria, together with proof levels, can be summarized as follows; In non-cardioembolic stroke and TIA, antiaggregant therapy is recommended to prevent stroke recurrence and to prevent other cardiovascular events (Class IA recommendation).The Asa dose is between 50-325 mg (Class IA recommendation) or clopidogrel 75 mg 1X1 (Class IIa B recommendation) should be administered (9).

Combined use of antiaggregant drugs was tried in non-cardioembolic stroke and TIA treatment, however the increased risk of intracerebral and extracerebral hemorrhage reduced the benefit of combined use of drugs. Dual antiaggregant use in coronary artery disease is widely recommended in guidelines (10), whereas studies are ongoing to determine indications in patients with ischemic stroke (11). It is stated that more aggressive antiaggregant treatment may be appropriate in high-risk patients in the acute period, however there are no data to support the application of different treatment strategies in acute and chronic periods in low-risk patients (12).

Dual antiaggregant therapy applications in patients with ischemic stroke began in the 1980s, and studies were conducted to determine whether the combination of dipyridamole and Asa was more beneficial than Asa alone. While some of the studies showed no additional benefit with the combination of dipyridamole and Asa, the ESPS2 (the European Stroke Prevention Study 2) study showed a relative risk reduction of 22 % in all major vascular events with combined use (50 mg Asa and 2 times 200 mg dipyridamole daily) compared to use of Asa alone. In the ESPRIT European Stroke Prevention in Reversible Ischemia Trial) study, the average dose of Asa is 75 mg and a risk reduction of 20 % was identified when used in combination with extended release dipyridamole. (7,13,14). It is stated in the guideline that a combination of Asa 25mg and ER (extended release) dipyridamole 200 mg (2X1) can be used to prevent non-cardioembolic stroke/TIA recurrence and other cardiovascular events (Class IB recommendation) (9), however ER-dipyridamole is not available in our country as in combination with Asa, whereas short-acting dipyridamole is available.

Studies with the combination of dipyridamole and Asa are studies regarding secondary provention not only in patients with acute stroke, but also in patients who have had a transient ischemic attack or minor stroke in the last 6 months. Similarly, the superiority of dual use to single use could not be revealed in combination therapy made with Asa and clopidogrel, mostly due to increased hemorrhagic side effects, in MATCH (Management of Atherothrombosis with Clopidogrel in High-risk patients) study which was applied not only in high-risk patients who admitted with acute stroke but also in patients who underwent stroke within last 3 months. MATCH is a randomized, double-blind, placebo-controlled study. 7599 high-risk patients with ischemic stroke or TIA were included in the study. The duration of treatment and follow-up was18 months, and the addition of Asa to clopidogrel leads to a nonsignificant reduction in major vascular events compared to the use of clopidogrel alone, while major bleeding was significantly increased (15,16).

In another study, the combination of clopidogrel (75 mg) and low-dose Asa (75-162 mg) was this time compared to low-dose Asa alone to reduce MI, stroke and cardiovascular mortality in patients at high risk for an atherothrombotic event (15603 patients). In the CHARISMA (Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events) study, the average follow-up period of the patients is 24

months. In patients with stable cardiovascular disease or multiple cardiovascular risk factors, the combination of Asa and clopidogrel did not lead to a significant reduction in MI, stroke and vascular-induced mortality rates when compared with Asa treatment. In addition, an increased risk of moderate to severe bleeding was observed (17).

The first study conducted to compare the effects of dual and mono antiplatelet therapies, and which includes only acute-stage patients, is the FASTER (Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence) study. In a study conducted on 392 patients with minor stroke or TIA who admitted within the first 24 hours after the onset of symptoms, the patients receiving clopidogrel (300 mg loading and maintenance with 75 mg) and Asa 81 mg were compared with the patients receiving Asa 81 mg only (by loading with 162 mg of Asa if receiving Asa for the first time). The period of study and treatment was 90 days. The study was terminated early due to inadequate number of patients; however, it was stated that dual therapy would significantly prevent stroke recurrence in high-risk patients and that the risk of hemorrhage would not reduce this benefit (18).

The main study that actually revealed the place of dual therapy in patients with TIA and minor stroke in acute period was the CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) study. The risk of recurrent stroke is high in patients who underwent TIA and minor stroke. After the first attack, almost 10-20% of the patients undergo a recurrent stroke within the first 3 months. This risk is particularly high in the first few days. Considering such facts, the treatment was initiated for the patients within first 24 hours in 2 different groups in this study. Both groups received 75-300 mg Asa at the discretion of the physician on the first day. The first group is clopidogrel-Asa group and received clopidogrel (300 mg loading on first day, 75 mg between 2nd and 90th days) an Asa (75 mg between 2nd and 21st days, and placebo Asa between 22nd and 90th days), and the second group received Asa (75 mg between 2nd and 90th days) and plasebo clopidogrel between 1st and 90th days).The stroke (ischemic or hemorrhagic) rates were compared within a 90-day follow-up period. The stroke was observed in 8.2 % of the patients in the dual treatment group, whereas this rate was 11.7 % in the Asa group. The difference between is statistically significant. Hemorrhagic stroke rate was found as 0.3 % in both groups. The incidence of moderate-severe hemorrhage was also not different between the two groups and was reported as 0.3 %. In summary, in the study, more effective results than Asa alone were obtained without increasing the risk of bleeding in the first 90 days with the use of short-term dual antiaggregant drugs (19). Thereupon, a meta-analysis was performed in 14 previous dual treatment trials (total 9012 patients), including MATCH and CHARISMA, that included the patients who were treated in the acute period only. When short-term use of dual and mono therapies are compared, it was found that dual antiplatelet treatment was more effective than single antiaggregant treatment to prevent early stroke recurrence without causing a significant increase in hemorrhagic side effects in anti-cardio-ischemic stroke and TIA patients who started treatment in the acute period (20). Depending on these results, the recommendation for the combination of Asa and clopidogrel in the first 90 days for TIA and minor stroke patients was included in the guideline, although the level of evidence (Class IIb B) was not very high (9).

The POINT (Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke) study is another comprehensive study to investigate the benefit of dual therapy in minor stroke and high-risk TIAs. In a multi-centered study involving 4881 patients, a portion of patients were randomized to receive Asa (50-325 mg per day) with clopidogrel (first day 600 mg loading dose, then 75 mg per day) or Asa alone in the same dose range. Patient groups were compared after 90 days in terms of ischemic stroke, MI and vascular death rates. While major ischemic events decreased by 25% in 90 days in patients receiving clopidogrel and Asa combination therapy, major hemorrhage rates were found to increase approximately twice (21). A detailed analysis of the POINT study shows that if combined use of clopidogrel and Asa is limited to 21 days, it is possible to reduce major ischemic events without significantly increasing the risk of hemorrhage. In case the dual therapy lasts for 21 days, maximum benefit (relative risk reduction 35 %) and minimum risk are in question (22). The explanation that the dual (together with Asa and clopidogrel) antiplatelet therapy, which begins

in the first 24 hours and lasts for 21 days in minor stroke, is beneficial for early secondary prevention (Class IIa B) was also mentioned in last published guideline on acute period therapy (5). New studies and evaluations in future guidelines may change the level of evidence.

According to the results of the meta-analysis of three acute period studies (FASTER, CHANCE, POINT) including 10447 minor stroke and TIA patients who received dual or mono antiplatelet therapy within the first 24 hours, the relative risk reduction in non-fatal recurrent stroke was found as 30 % and the absolute risk reduction was found as 1.9 %. There was no significant effect on all-cause mortality, however the risk of extracranial hemorrhage was found to be 1.7 times higher (23). The results of this meta-analysis can be summarized as follows; When 1000 patients, in TIA and minor stroke, are administered with clopidogrel and Asa dual treatment in the first 24 hours, 20 strokes are prevented, and the risk of moderate to severe bleeding increases in 2 out of 1000 patients with TIA and minor stroke. Discontinuation of dual treatment within 21 days, and even within 10 days if possible, leads to increased benefit and minimizes bleeding.

5590 patients with a mean age of 64 ± 13 years were included in another study, in which clopidogrel and Asa were used in combination and a comparison was made with single Asa use, and similar to previous studies, dual use was found to be significantly more beneficial in non-cardioembolic stroke cases who admit with minor stroke. The stroke recurrence, MI and vascular mortality rates were found lower in the patients who received dual therapy in the first 3 months of therapy. In this study, unlike previously conducted dual trials, the subgroup evaluations were made and the benefit was found more significant especially in the group without small vascular disease, in those who had previously received antiaggregant therapy and in elderly patients (24).

In acute ischemic stroke, in the patients whose etiology is non-cardioembolic, randomized trials demonstrated that dual therapy is more beneficial in patients with minor stroke and TIA than single therapy (19,21), however, in these studies, the patients with unknown etiology, lacunar stroke patients with small vessel disease and atherothrombotic stroke patients were investigated together. In SPS3 (Secondary Prevention of Small Subcortical Strokes) study which was conducted on lacunar stroke patients only, the use of clopidogrel in combination with Asa did not lead to a significant reduction in the recurrent stroke rate and a significant increase was observed in the risk of bleeding and mortality rate. The rate of major hemorrhage (2.1 % per year) during dual antiaggregant therapy increased almost twice when compared to single treatment (1.1 % per year) (25). In 20-30 % of patients with lacunar stroke, an early neurological deterioration occurs in the first days after stroke. An effective treatment strategy in these patients is unclear. In a recent study, the standard therapy and dual antiaggregant therapy were compared on 458 patients with progressive lacunar stroke, and the patients receiving dual treatment (68 %) showed a better clinical improvement than the patients receiving standard treatment (36 %). While no clinical fluctuation was observed in 79 % of those receiving dual treatment, this rate was found to be 33% in those who did not receive dual treatment, and these findings were interpreted as the positive effect of dual treatment (26).

Recurrence of stroke is greater in patients with large atherosclerosis than in small vessel disease. A more intensive treatment can be more effective to prevent thrombus formation in the atherosclerotic vessel. In CARESS (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis) study, microembolic signals were examined by transcranial Doppler in patients with symptomatic carotid stenosis, it was shown that these signals decreased significantly in patients who received dual treatment (11,27). How would the outcomes be when the patients only with symptomatic major vascular disease or atherothrombotic stroke are included in the study were examined in another study. In this multicentre but non-randomized study based on retrospective evaluation, it was examined if there is any difference between use of Asa only (3031 patients) and use of Asa and clopidogrel combination (2903 patients) in atherosclerotic strokes. At the end of one year, stroke recurrence and mortality rates were compared between the two groups, and no difference was observed between dual therapy and single therapy in terms of stroke recurrence, and the mortality rates were found significantly decreased. However, since the study was conducted in a very heterogeneous

patient group and was a retrospective evaluation, it was stated that the results of the study should be interpreted mindfully and randomized studies are needed for this indication (11).

In addition to comparison of dual and single therapy in different etiologies, researches are also being conducted on the choice of therapy according to different infarct apperarances. According to the sub-group evaluations of the CHANCE study, it was suggested in diffusion-weighted imaging that patients with multiple acute infarcts benefit more from dual therapy without a significant increase in the risk of bleeding, compared to patients with single acute infarct (28).

Ticagrelor, one of new antiaggregant drugs, was used mainly in acute coronary syndrome, whereas stroke patients are not sufficiently studied yet. A study where ticagrelor and Asa were compared was conducted on patients with TIA and minor stroke. In the SOCRATES (Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes) study, 9600 patients with TIA and minor stroke were initiated with ticagrelor (180 mg loading, 90 mgX2 maintenance treatment), Asa (300 mg loading, 100 mg maintenance treatment) within the first 24 hours. The primary endpoints were ischemic stroke, MI, vascular death difference in the first 90 days. In this study, the superiority of ticagrelor over Asa was investigated, but the results were not found different from Asa (29). Ticagrelor is not recommended instead Asa in the guideline for minor stroke in acute period. In subgroup evaluations, ticagrelor treatment was superior to Asa in terms of the incidence of stroke, MI and vascular death in the first 90 days in patients with ipsilateral atherosclerotic stenosis (30), however there is no guideline recommendation for the use in this indication yet.

THALES (Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and Asa for Prevention of Stroke and Death) is a new study intended to be conducted with ticagrelor. The number of patients intended to be included in the study is 13000. It will be investigated whether there is a difference between the use of Asa and ticagrelor combination or the use of Asa alone within the first 24 hours in patients with a minor stroke over the age of 40 with an NIH stroke score of less than 5. The planned completion date of the study is December 2019 (31).

A multi-centered, randomized trial was planned on the basis of the following question: “Is it possible to go beyond the dual antiaggregant treatment in patients with ischemic stroke and to obtain more efficient outcomes by using more commonly used antiaggregant medications together with the three treatments that are recommended in today's guidelines?”. The TARDIS (Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke) study was conducted by administering to the patients (3096 patients) within 48 hours an intense therapy (Asa 75 mg, clopidogrel 75 mg and dipyridamole 200 mg twice a day) or a therapy compliant with the guidelines (only clopidogrel or a combination of Asa and dipyridamole). Triple intensive therapy (i.e., concomitant use of Asa, clopidogrel and dipyridamole) did not lead to a significant change in stroke recurrence and severity compared to the use of clopidogrel or Asa and dipyridamole alone, whereas the rate of major bleeding was increased. The study was terminated early and it was recommended not to apply triple therapy in routine clinic practice (32).

CONCLUSION

In conclusion, the treatment options for secondary prevention in acute ischemic stroke are limited. Early and short-term use of dual antiplatelet therapies become widespread in order to reduce mortality and dependence rates, reduce stroke recurrence and prevent vascular complications in patients with minor stroke and transient ischemic attack. The number of reviews and meta-analyzes made on this subject increased in recent years (23,33,34). Today, the strongest suggestion is to initiate within the first 24 hours and use dual antiplatelet treatment together with clopidogrel and aspirin for 10-21 days in patients with minor stroke and TIA, and to continue thereafter with single medication. In major stroke, the dual therapy is not recommended as it increases the risk of intracranial hemorrhage. Our knowledge and experience on the benefits of dual therapies in ischemic stroke and patient selection is gradually increasing by virtue of new drugs and new studies.

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