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Application of Instaclop Plus (Clopidogrel+Aspirin) in Treatment and Prevention of Thrombosis

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Abstract: *The article describes the effectiveness and safety of use in patients of the main class of modern antiplatelet agents used in the clinical practice of a cardiotherapist, interventional cardiologist, general practitioner in the treatment of coronary heart disease and other pathologies of the cardiovascular system based on data from long-term studies conducted in foreign countries and in Uzbekistan. According to these studies, devoted to studying the effectiveness of the combined drug clopidogrel + aspirin, the main clinical and pharmacological descriptions of the drug Instaclop plus, often used in Uzbekistan, are given.*

Key words: *double antiplatelet therapy, clopidogrel, aspirin, Instaclop plus, clinical pharmacology, safety, effectiveness*

Introduction

The history of medicine has preserved for us not only brilliant theories that determined progress in the knowledge of diseases, not only research methods, such as x-rays and electrocardiography, which even today determine successes in diagnosis. She also preserved a number of medicines, without which it is difficult to imagine the healing process both in the past and in the present. Digoxin, nitroglycerin, acetylsalicylic acid (ASA) helped our teachers maintain the health of patients, and today they help us in the fight against a number of serious diseases [6, 20, 27].

Over the years, the progress of science reveals more and more new facets of their action. Only fifty years after the introduction of ASA into widespread practice as an analgesic and anti-inflammatory agent, its antiplatelet properties were discovered, which made it possible to begin its use to prevent thrombosis. And today it is even difficult to say what attracts doctors more to this drug - its anti-inflammatory or antiplatelet effect [3, 17, 23].

The benefit of combined use of clopidogrel and ASA, which is now commonly called dual antiplatelet therapy, for non-ST segment elevation ACS was convincingly proven in a large randomized, double-blind, placebo-controlled trial, the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial. In the study, 12,562 patients with non-ST-segment elevation ACS, with a mean age of 64 years, were randomized into two groups within 24 hours of symptom onset. Of these, 6,259 patients, in addition to ASA (from 75 to 325 mg/day), were prescribed clopidogrel (loading dose 300 mg, then 75 mg once a day), and 6,303 patients received aspirin + placebo. The average duration of

follow-up according to the study results was 9 months. Cardiovascular events such as sudden death, non-fatal MI and stroke were significantly less frequently recorded in the group of patients receiving combined treatment with clopidogrel + ASA. Moreover, the advantage of clopidogrel was noted already in the first 24 hours of treatment. In the dual-drug group, there was less recurrence of severe pain during hospitalization, fewer cases of heart failure, and less need for myocardial revascularization. The main disadvantage of the aspirin + clopidogrel combination was also identified - an increase in the number of serious bleedings (3.7 compared with 2.7% in the placebo group, RR (relative risk) 1.38; p = 0.001). However, it is important that the incidence of life-threatening bleeding (including hemorrhagic stroke) did not differ significantly between the study groups (2.1% and 1.8%; p = 0.13) [5, 13, 24].

The PCI-CURE study included 2658 patients who underwent balloon angioplasty or coronary artery stenting. The duration of observation and administration of clopidogrel after PCI was approximately 12 months. The results obtained demonstrated clear advantages of dual angioplatelet therapy in interventional methods of treating coronary atherothrombosis. At the same time, a decrease in the number of both early events and secondary outcomes was noted [2, 18, 21].

Finally, the preference for long-term (12 months) clopidogrel therapy in patients after PCI was convincingly confirmed in the CREDO (Clopidogrel for the Reduction of Events During Observation) study. The protocol included 2,116 patients who underwent PCI, most of whom underwent it for ACS. Long-term (for 1 year) use of the combination of clopidogrel with ASA led to a reduction in the number of deaths, MI and strokes by 26.9% (p = 0.02) compared with the group receiving ASA and placebo. This study also found that treatment efficacy was increased when a loading dose of clopidogrel (300 mg) and ASA (325 mg) was administered at least 6 hours before coronary angioplasty, and later administration of clopidogrel had no effect on final outcomes. points [8, 25].

The European Society of Cardiology recommends using a two-component regimen for 12 months even in those patients who do not undergo stent placement [4, 19, 32].

Interestingly, in the latest edition of the ACC/AHA consensus recommendations, PCI with stenting is considered as the main method of therapy and, accordingly, thienopyridines, and primarily clopidogrel as part of two-component therapy, are considered as a mandatory component of treatment for at least 12 months. After this period, in the absence of additional indications, ASA should be used indefinitely, essentially for life or until side effects appear [1, 10, 22].

Of course, doubts remain regarding the effectiveness and, to a greater extent, safety of the use of triple antithrombotic therapy after angioplasty and stenting in patients initially taking indirect anticoagulants. As noted above, the risk of bleeding when taking aspirin, clopidogrel and warfarin simultaneously is assessed as very high. In this regard, all modern recommendations contain a clause stating that implantation of drug-eluting stents should be avoided in patients who require constant use of indirect anticoagulants [7, 26].

The benefit of combined use of clopidogrel and ASA, which is currently called a two-component ATT regimen, in non-ST segment elevation ACS was convincingly proven in a large randomized, double-blind, placebo-controlled trial, the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial. In the study, 12,562 patients with non-ST-segment elevation ACS, with a mean age of 64 years, were randomized into two groups within 24 hours of symptom onset. Of these, 6259 patients, in addition to ASA (from 75 to 325 mg/day), were prescribed clopidogrel (loading dose 300

mg, then 75 mg once a day), and 6303 patients received aspirin + placebo. The average duration of follow-up according to the study results was 9 months. Cardiovascular events such as sudden death, non-fatal myocardial infarction and stroke were significantly less frequently recorded in the group of patients receiving combination treatment with clopidogrel + ASA (RR in the clopidogrel group compared with the placebo group was 0.8; 95% confidence interval (CI) 0.72–0.90; $p < 0.001$). Moreover, the advantage of clopidogrel was noted already in the first 24 hours of treatment. In the dual-drug group, there was less recurrence of severe pain during hospitalization, fewer cases of heart failure, and less need for myocardial revascularization. The main disadvantage of the aspirin + clopidogrel combination was also identified - an increase in the number of serious bleedings (3.7 compared with 2.7% in the placebo group, RR 1.38; $p = 0.001$). However, it is important that the incidence of life-threatening bleeding (including hemorrhagic stroke) did not differ significantly between the study groups (2.1% and 1.8%; $p = 0.13$) [11, 28].

The PCI-CURE study included 2658 patients who underwent balloon angioplasty or coronary artery stenting. The duration of observation and administration of clopidogrel after PCI was approximately 12 months. The results obtained demonstrated clear advantages of the two-component regimen in interventional methods of treating coronary atherothrombosis. At the same time, there was a decrease in the number of both early (primary) events (death, MI, repeated revascularization in the first 30 days) and secondary outcomes (death + MI within 400 days of observation) [16, 29].

Finally, the preference for long-term (12 months) clopidogrel therapy in patients after PCI was convincingly confirmed in the CREDO (Clopidogrel for the Reduction of Events During Observation) study. The protocol included 2116 patients who underwent PCI, most of whom underwent it for ACS. Long-term (for 1 year) use of the combination of clopidogrel with ASA led to a reduction in the number of deaths, MI and strokes by 26.9% ($p = 0.02$) compared with the group receiving ASA and placebo. This study also found that treatment efficacy was increased when a loading dose of clopidogrel (300 mg) and ASA (325 mg) was administered at least 6 hours before coronary angioplasty, and later administration of clopidogrel had no effect on final outcomes. points [12, 30].

Currently, interventional cardiology is one of the main areas of application of clopidogrel. Most controlled clinical trials have demonstrated significant improvements in the outcomes of revascularization procedures in patients with ACS treated with clopidogrel. Long-term (12 months) use of clopidogrel after PCI is associated with a lower incidence of the composite endpoint (CV death + MI + revascularization), as well as a 25% reduction in the relative risk of death and MI ($p = 0.03$ and $p = 0.047$, respectively) [15].

The randomized multicenter PCI-CLARITY trial (PCI-CLopidogrel as Adjunctive ReperfusIon TherapY) demonstrated the beneficial effect of clopidogrel in patients undergoing PCI and stenting for ST-segment elevation MI [17].

This protocol was part of the larger CLARITY–Thrombolysis in Myocardial Infarction (TIMI) trial 28, which analyzed outcomes in 1863 patients who received thrombolytic therapy for acute ST-segment elevation MI. Study participants were randomized to receive clopidogrel (loading dose 300 mg, then 75 mg/day until angiography) or placebo while receiving thrombolysis. All study participants also received ASA. Coronary angiography (CAG) was performed within 2 to 8 days (on average 3.5 days) after patients were included in the study. All patients who required stenting were prescribed clopidogrel in the same dosages (300 + 75 mg/day) from the moment of coronary angiography. Treatment with clopidogrel prior to coronary intervention significantly reduced the

incidence of the primary composite endpoint (CV mortality + recurrent myocardial infarction + ischemic stroke) from the time of PCI to 30 days after randomization (RR 0.54; 95% CI 0.35 -0.85; p = 0.008). The incidence of MI and stroke before PCI was also significantly lower in the clopidogrel group (RR 0.62; 95% CI 0.40–0.95; p = 0.03). Overall, the dual regimen compared with ASA monotherapy significantly reduced mortality from cardiovascular causes, MI, and stroke within 30 days of randomization (RR 0.59; 95% CI 0.43–0.81; p = 0.001). At the same time, the frequency of major and minor bleedings during combination therapy and isolated use of aspirin was practically the same (2.0 and 1.9%, respectively; p > 0.99) [14, 31].

The high efficacy of the two-component regimen (compared to aspirin monotherapy) in patients undergoing PCI with stenting for ACS was confirmed by the results of a meta-analysis of 8 large randomized trials published before 2006. A total of 91,744 patients were included in the analysis. A dual ATT regimen in patients undergoing invasive revascularization compared with ASA monotherapy reduced the relative risk of the combined endpoint (death + recurrent MI + stroke) by 34%. However, combination therapy was associated with a significant increase in the risk of major bleeding when the study duration exceeded 1 month (RR 1.80; 95% CI 1.40–2.30) [9, 22].

In contrast to invasive interventions in patients with ACS, the effectiveness and safety of the use of clopidogrel before planned interventions on the coronary vessels has been studied to a lesser extent. According to individual publications, the administration of clopidogrel before PCI does not lead to a significant additional reduction in platelet aggregation in patients with stable angina receiving aspirin. In this regard, some authors express the opinion that in patients with chronic coronary artery disease and at low risk, it is possible to do without additional ATT after planned PCI and stenting of the coronary arteries. However, the results of the CREDO study indicate an advantage of the two-component regimen over ASA monotherapy in patients undergoing elective invasive surgery. This protocol demonstrated that the use of clopidogrel is associated with a reduction in the rate of repeat revascularization of the target coronary artery [16, 33].

Currently, the advisability of using clopidogrel before and after elective stenting of the coronary arteries is beyond doubt. This is reflected in the latest editions of all relevant guidelines for percutaneous coronary intervention (ACC/AHA, ESC) [8].

Based on the pathogenesis of the disease, it is obvious that in patients with ACS without ST segment elevation, antiplatelet agents should be prescribed as early as possible, simultaneously with the relief of a painful attack. In this regard, in the absence of contraindications, the first dose of ASA is prescribed to all patients with ACS without ST segment elevation as early as possible. The latest version of the recommendations of the European Society of Cardiology clearly indicates the advisability of parallel administration of the first dose of aspirin to all such patients should be given a loading dose of clopidogrel, which is 300 mg, followed by a maintenance dose of 75 mg for 12 months. It should be noted that in terms of the level of evidence (IA) this point of the recommendations is not inferior to the postulate about the need to take aspirin. The use of the above loading dose of clopidogrel is due to the fact that in this case, effective inhibition of platelet aggregation is achieved within 4–6 hours, whereas when prescribing 75 mg of the drug, it manifests itself only after 3–5 days [14].

Conclusion

Clopidogrel + Aspirin is still considered the preferred combination of dual antiplatelet therapy both in acute conditions and in long-term prevention of cardiovascular diseases. Its clinical effectiveness

in reducing the incidence of MI, ischemic stroke and vascular death in various groups of high-risk patients is confirmed by the results of multiple retrospective studies and meta-analyses. At the same time, the need for long-term dual antiplatelet therapy dictates the requirements for its safety.

All of the above requirements are met by the drug Instaclop Plus, which is produced at the modern Ajanta Pharm plant (India). Instaclop plus is available in tablets, in a dose of 75+75 mg and, which is important these days, has a price affordable for most patients in Uzbekistan.

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