Bleeding complications after percutaneous coronary interventions in patients treated with abciximab in relation to dose of clopidogrel

Powikłania krwotoczne po przezskórnych interwencjach wieńcowych u pacjentów leczonych abciksimabem w zależności od zastosowanej okołozabiegowo dawki klopidogrelu

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Abstract

Background: Administration of potent and fast-acting medications inhibiting platelet adhesion and aggregation is crucial to improve outcomes of percutaneus interventions.

Aim: To compare the incidence of bleeding complications in patients treated with abciximab and different doses of clopidogrel. Additonal aim of the study was to compare the decrease of hemoglobin concentration.

Methods: Medical records of patients who underwent invasive procedure between 2003 and 2006 were retrospectively analyzed. Patients treated with abciximab in standard dose and 75 mg or 300 mg of clopidogrel as the concomitant therapy were included. Exclusion criteria included: myocardial infarction caused by in-stent thrombosis, previous treatment with thienopyridine, participation in clinical trial with medication influencing the coagulation cascade, application of IIb/IIIa receptor inhibitor other than abciximab, lack of data in electronic records. For the purpose of the analysis of changes in the haemoglobin concentration patients who underwent surgical procedure were exluded.

Results: Study group consisted of 324 patients, of whom 165 received 75 mg of clopidogrel and 159 received 300 mg of clopidogrel. Following complications were registered: haematoma of the arterial access site (diagnosis based on ultrasonography – organized hematoma exceeding 3 cm in diameter), pseudoaneurysm, retroperitoneal haematoma, gastrointestinal bleeding, haematuria. These complications was present in 6.7% patients who received 75 mg of clopidogrel and 11.9% patients who received 300 mg of clopidogrel ($p = 0.1$). Haemoglobin concentration decreased by 1.35 (0.6-2.2) g/dl in 75 mg group and by 1.8 (0.9-2.6) g/dl in 300 mg group ($p = 0.046$), respectively.

Conclusions: Administration of 300 mg of clopidogrel together with abciximab is not significantly related to a higher frequency of bleeding complications, but it is related to a higher decrease of haemoglobin concentration in comparison to administration of 75 mg of clopidogrel. Special awareness concerning bleeding complications is needed when applying aggressive antiplatelet therapy.

Key words: abciximab, clopidogrel, percutaneous coronary intervention, bleeding complications

Streszczenie

Wstęp: Podanie skutecznych i szybko działających leków hamujących agregację i adhezję płytek krwi ma podstawowe znaczenie dla poprawy wyników interwencji przezskórnych.

Cel: Porównanie częstości występowania powikłań krwotocznych u chorych leczonych z powodu zawału serca z uniesieniem odcinka ST (STEMI) metodą pierwotnej angioplastyki wieńcowej, u których zastosowano leczenie abciksimabem oraz klopidogrelem w zależności od zastosowanej okołozabiegowo dawki klopidogrelu. Dodatkowym celem było porównanie spadku stężenia hemoglobiny.

Metody: Analizie retrospektywnej zostali poddani pacjenci leczeni inwazyjnie z powodu STEMI w latach 2003–2006. Kryterium włączenia było podanie abciksimabu w standardowej dawce, jako bolus i następnie wlew oraz klopidogrelu w dawce 75 mg lub 300 mg, jako farmakoterapii wspomagającej przezskórną interwencję wieńcową.

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Kryteriami wyłączenia były: zawał z powodu zakrzepicy w stencie, wcześniejsze leczenie tiklopidyną lub klopidogrelem, udział w badaniu klinicznym z lekami wpływającymi na układ krzepnięcia, użycie innego niż abciksimab blokera receptora IIb/IIIa, brak danych o procedurach i przebiegu choroby w dokumentacji elektronicznej. W podgrupach, w których analizowano spadek stężenia hemoglobiny, wykluczono pacjentów poddanych zabiegowi chirurgicznemu.

Wyniki: Do analizy włączono 324 osoby, 165 otrzymało 75 mg klopidogrelu, a 159 dawkę 300 mg. W obu badanych grupach wyodrębniono następujące powikłania krwotoczne: krwiak w miejscu wkłucia (diagnoza oparta na ultrasonografii – zorganizowany krwiak o średnicy powyżej 3 cm), tętniak rzekomy, krwiak zaotrzewnowy, krwawienie z przewodu pokarmowego, krwiomocz. Jakiekolwiek z wymienionych powikłań wystąpiły u 6,7% pacjentów, którzy otrzymali 75 mg klopidogrelu oraz u 11,9% pacjentów, którzy otrzymali 300 mg klopidogrelu (p = 0,1). Spadek stężenia hemoglobiny wyniósł 1,35 (0,6–2,2) g/dl w grupie przyjmujących 75 mg klopidogrelu oraz 1,8 (0,9–2,6) g/dl w grupie przyjmujących 300 mg klopidogrelu (p = 0,046).

Wnioski: Podanie klopidogrelu w dawce 300 mg w połączeniu z abciksimabem nie wiąże się z istotnie większą częstością występowania powikłań krwotocznych, wiąże się z kolei z większym spadkiem stężenia hemoglobiny we krwi niż w przypadku podania klopidogrelu w dawce 75 mg. Stosowanie agresywnej terapii przeciwzakrzepowej wymaga zwrócenia szczególnej uwagi na możliwość wystąpienia zwiększonego ryzyka powikłań krwotocznych.

Słowa kluczowe: abciksimab, klopidogrel, przezskórna interwencja wieńcowa, powikłania krwotoczne

Introduction

Administration of potent and fast-acting drugs inhibiting platelet adhesion and aggregation plays a crucial role to improve outcomes of primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI). Current guidelines on pharmacotherapy recommend the concomittant use of three antiplatelet drugs: aspirin, clopidogrel and glycoprotein (Gp) IIb/IIIa inhibitors. It is recommended to administer at least 300 mg and preferably 600 mg of clopidogrel prior to primary PCI. According to the current guidelines the highest class of recommendations among Gp IIb/IIIa inhibitors is atributted to abciximab. Its administration is recommended in STEMI and in non-ST elevation myocardial infarction (NSTEMI) [1-3].

Efficacy of abciximab in primary PCI in STEMI was confirmed in many randomized clinical trials. Analysis of RAPPORT [4], ISAR-2 [5], ADMIRAL [6] and CADILLAC [7] trials demonstrated that the use of abciximab for primary PCI in STEMI reduces the frequency of death, recurrent myocardial infarction and the need of repeat revascularization at 30-day and 6-month follow-up.

Another drug which influenes coagulation processess and is recommended for PCI is unfractionated heparin. According to ESC 2008 guidelines it should be administered i.v. as a bolus (100 IU/kg) and adjusted to maintain ACT (Activated Clotting Time) between 250-350 s. In case of the concomittant use of Gp IIb/IIIa inhibitors it is recommended to reduce the dose of heparin to 60 IU/kg to maintain ACT between 200-250 s.

The use of antiplatelet and antithrombotic drugs increases the risk of bleeding complications. According to various studies those complications may be observed in up to 30% of patients treated invasively for acute coronary syndrome [8]. Several modifiable and unmodifiable risk factors were indentified. Independent risk factors of bleeding in patients with acute coronary syndromes include: advanced age, high sytolic blood pressure, increased creatinine concentration and previous stroke. Until now only few studies analyzed the number of complications in the arterial access site in relation to impairment of haemostasis in patients who received abciximab. Konstance et al. reported presence of pseudoaneurysm in 2.3% of cases, arteriovenous fistula in 0.4% and retroperitoneal haematoma in 0.2% [9]. Following risk factors of these complications were identified: advanced age, female sex, stent use, 6 F or larger vascular sheath, the use of mechanical preassure device, late removal of vascular sheath and number of stents and balloons used [8].

The aim of the study was to evaluate the frequency of bleeding complications in patients undergoing percutaneous coronary intervention who received treatment wit abciximab and clopidogrel in relation to dosing of clopidogrel. Bleeding at the arterial access site and mucous membrane bleeding were evaluated. Additional aim was to compare the maximal decrease of hemoglobin concentration registered during hospitalization in the studied group.

Methods

This retrospective analysis included patients treated with primary PCI for STEMI in the 3rd Division of Cardiology of the Silesian Medical University in Katowice between 2003-2006. Inclusion criteria consisted of administration of standard dose of abciximab (bolus plus infusion) in addition to 75 or 300 mg of clopidogrel as pharmacotherapy supporting percutaneous coronary intervention. According to guidelines 75 mg of clopidogrel was a routinely used dose between 2003 and 2005.

Patients with in-stent thrombosis as a cause for intervention and patients previously treated with ticlopidine or clopidogrel were excluded from the study.

All statistical tests were performed with the use of STATISTICA for Windows 8.0 package. Statistical

Table 1. Frequency of complications in both groups
Tabela 1. *Częstość powikłań w obu badanych grupach*

Complication	75 mg n = 165	300 mg n = 159	All n = 324
None, n (%)	154 (93.3)	140 (88.1)	294
Pseudoaneurysm, n (%)	2 (1.2)	3 (1.9)	5
Haematoma of the arterial access site, n (%)	6 (3.6)	12 (7.6)	18
Retroperitoneal haematoma, n (%)	0	1 (0.6)	1
Gastrointestinal bleeding, n (%)	2 (1.2)	3 (1.9)	5
Haematuria, n (%)	1 (0.6)	0	1

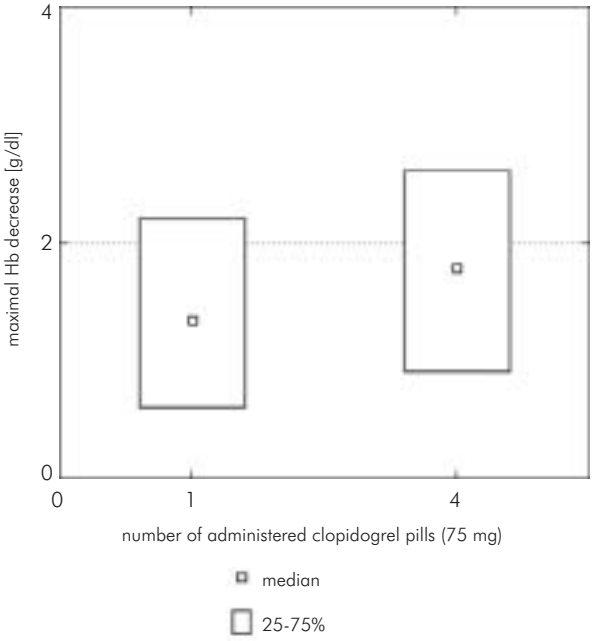

Fig. 1. Maximal deacrease of haemoglobin (Hb) concentration in both groups
Ryc. 1. *Maksymalny spadek stężenia hemoglobiny w badanych grupach*

significance level was set at $p < 0.05$. The Kolmogorov--Smirnov and the Shapiro-Wilk tests were applied to check for normality of distribution. The Student's t-test was used to compare means between groups for variables with confirmed normal distribution. Variables without normal distribution were presented as medians and interquartile ranges and compared with means of the Mann-Whitney U test. Differences between categorical variables were analyzed with the use of the χ^2 test.

Results

The analysis included 324 patients, of whom 165 received 75 mg of clopidogrel and 159 received 300 mg of clopidogrel. There were no differences between those two groups in terms of sex and age. Mean age of patients was 59.3 ± 11 and 58.7 ± 11 years respectively, 73.3% and 74.2% of patients in each group were male. Registered complications and their frequency in both groups are presented in table 1. Haematoma of the aterial access site was defined as a skin decoloration at the site of femoral artery puncture exceeding 3 cm in diameter. Presence of haematoma of the arterial access site had to be confirmed with ultrasonography.

The predifined complications were observed in 6.7% patients who received 75 mg of clopidogrel and in 11.9% of patients who received 300 mg of clopidogrel ($p = 0.1$).

Decrease of heamoglobin concentration was analyzed in 199 patients who had at least two blood morphology assessments present in the electronic database. There was no statistical difference between this group and the rest of patients in terms of sex (72.9 vs. 69.8% male, $p = 0.4$) and age (59.7 vs. 59.7%, $p = 0.99$). Maximal decrease of haemoglobin concentration based on the available assessments was calculated for each patient. The subgroups treated with 75 and 300 mg of clopidogrel consisted of 72 and 127 patients respectively. Median decrease of haemoblobin concentration was 1.35 (0.6--2.2) g/dl and 1.8 (0.9-2.6) g/dl ($p = 0.046$) respectively (fig. 1).

Discussion

Glycoprotein IIb/IIIa is a fibrynogen, fibronectin, vitronectin, von Willebrand factor and thrombospondin binding receptor [10]. This type of affinity makes this receptor a very important element of platelet adhesion and aggregation. Treatment of acute coronary syndrome influences many pathways which finally lead to activation of glycoprotein IIb/IIIa.

Adenosine diphosphate (ADP) pathway in inhibited by thienopyridines, while thromboxane A_2 (TXA_2) dependent pathway is blocked by aspirin (ASA). Administration of monoclonal antibody blocking the common pathway of the above processes exerts a strong antiaggregatory effect. Awerness of this fact poses a question on the safety of the combination of different drugs ultimately affecting the key physiological pathway.

In the literature there are reports regarding bleeding complications on abciximab, as for example results of the first study evaluating the use of abciximab – the EPIC trial [11]. Major bleeding complications in patients who received abciximab on top of aspirin and heparin occured three times more often in comparison to patients who received placebo (3.3 vs. 10.6%). Patients in the abciximab group three times more often required transfusion (7.5 vs. 16.8%). Literature analysis shows reports on the effects of combined use of loading dose of clopidogrel and abciximab. Pharmacodynamic assumptions that abciximab leads to more complete inhibition of platelet aggregation

were clinically confirmed [12]. Current guidelines unequivocally recommend the administration of loading dose of at least 300 mg, and preferably 600 mg of clopidogrel [2, 3]. Therefore clinical trials do not include arms with reduced clopidogrel dosing and it is the role of retrospective analyses of registries conducted before the implementation of the new guidelines to demonstrate the frequency of complications in relation to various doses of clopidogrel and the use of abciximab.

Current analysis presents complications registered at the access site as well as other clinically relevant symptoms of impaired haemostasis such as bleeding from the mucous membranes. This strategy calls into several questions. The most important one is to what extent local complications depend on inhibition of coagulation processess on one side and on the technical aspects of the procedure on the other (such as the type of devices used). Both groups come from the same center and reducing the possibility of large differences in devices used for the procedures. Therefore detailed analysis of the devices used with respect to the number of patients included in the registry would not bring new statistically significant observations.

The disadvantage of the chosen strategy is the incomparability of the clinical significance of the registered complications and their influence on prognosis when analyzing complications such as haematuria and retroperitoneal bleeding. Nevertheless the sum of registered complications in the two demographically comparable groups was found to be different. Despite statistically insignificant difference and a trend towards higher frequency of complications it seems reasonable to plan a larger prospective studies evaluating safety of 300 vs. 600 mg loading dose of clopidogrel in patients who receive abciximab.

Statistically significant difference between mean decrease of haemoglobin concentration in both groups treated with two doses of clopidogrel is a more objective marker independent from the visually estimated extent of bleeding.

Additon of abciximab to heparin increases the risk of minor bleeding, but does not influence the risk of major bleeding [13]. There was a relation between prolongation of the clotting time on heparin measured with ACT and the frequency of bleeding complications in 48-hours follow-up [14]. This relation was mainly caused by minor bleeding complications and there was no correlation with major bleeding events. Current analysis did not include information on dosing of heparin rutinely used for percutaneous interventions, because this factor was considered independent from the dose of clopidogrel and deemed nonconfounding in the statistical analysis. Due to this consideration and a standarization of heparin dosing adjusted to ACT it was presumed that mean heparin dose is similar in both studied groups.

Conclusions

Administration of 300 mg of clopidogrel together with abciximab is not significantly related to a higher frequency of bleeding complications, but it is related to a higher decrease of haemoglobin concentration in comparison to administration of 75 mg of clopidogrel. Special awareness concerning bleeding complications is needed when applying aggressive antiplatelet therapy.

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