THE INFLUENCE OF ANTI-PLATELET AND ANTITHROMBOTIC TREATMENT ON THE CLINICAL COURSE OF BLEEDING INTO THE LUMEN OF ALIMENTARY TRACT UPPER SEGMENT

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The most frequently used drugs which may cause bleeding into the lumen of alimentary tract include: acetylsalicylic acid (ASA), ticlopidine/clopidogrel and acenocoumarol.

The aim of the study was to analyze the frequency of the occurrence of bleeding into the lumen of alimentary tract upper segment (gopp) in patients taking anti-platelet drugs and oral anticoagulants, treated at the surgical department.

Material and methods. The study covered a group of 164 patients treated at the Clinical Surgery Department of the Provincial Hospital in Kielce over the years 2006-2009. They were consecutive patients admitted to hospital with the initial diagnosis of bleeding into the lumen of gopp. The diagnosis was made on the basis of medical history, clinical examination and additional investigation. In all patients within 24-48 hours after the admission endoscopy of gopp was performed.

Results. 164 patients with symptoms of bleeding into the lumen of gopp were treated. Among them there were 94 men (57%) as well as 70 women (43%). The average age was 61.8 years (from 23 to 91 years). In this group 24.4% (40/164) patients took drugs influencing coagulation system (acetylsalicylic acid, clopidogrel and/or acenocoumarol). In the subgroup taking the drugs mentioned above were 21 men (52.5%) and 19 women (47.5%). The average age was 73.6 years (from 48 to 91 years). Among patients taking drugs influencing hemostasis system 23 patients took ASA preparations, ticlopidine/clopidogrel – 5 patients and acenocoumarol – 12 patients. 8 patients took more than one drug, most frequently ASA and ticlopidine/clopidogrel, 1 patient took three drugs. 6 deaths were reported in the group taking drugs. Mortality rate was 15% (6/40). Among the deceased patients significantly lower (p<0.001) concentration of hemoglobin at the admission can be noticed (average concentration of Hb reached 6.1 g/dl) as well as non-interchangeably higher (p=0.13) average age of patients (average age of the deceased patients was 77.2 years). All the deceased patients were admitted to hospital with hypovolaemic shock. Results were statistically analyzed by the use of the test for comparison of two proportions and the t-Student test for the difference in expected values.

Conclusions. Bleeding into the lumen of gopp induces considerable mortality, especially in patients with low hemoglobin concentration and hypotension at the admission to hospital. During the treatment of a patient with bleeding into the lumen of gopp a compromise between the risk of cardiovascular complications and the risk of death due to bleeding should be searched for.

Key words: acetylsalicylic acid, bleeding into the lumen of alimentary tract

Patients who take drugs which may cause symptomatic bleeding into the lumen of alimentary tract are often hospitalized at surgical departments. These drugs are taken according to doctor’s recommendations but also under the influence of media advertisements. Among them are: acetylsalicylic acid (aspirin), ticlopidine and clopidogrel, acenocoumarol.
Aspirin is an anti-platelet drug used in primary and secondary prevention of cardiac infarction. Its era started in 1971 when the mechanism of action through irreversible inhibition of the activity of cyclooxygenase 1 (COX-1) was discovered. The effect is the inhibition of the synthesis of prostaglandin G2/H2, including thromboxane A2. It was the basis for the application of acetylsalicylic acid as an inhibitor of platelets activity. Twenty-four hours dose of aspirin 75 mg blocks platelets activity for a few days. Non-steroidal anti-inflammatory drugs (NLPZ) together with aspirin are the most frequently used drugs in the world. Almost 50 000 tons of acetylsalicylic acid is produced annually in the world. Aspirin has been known and used for almost 100 years. Moreover, aspirin is very commonly used by people who bought it themselves or for whom it was prescribed by their family doctor. The dose of aspirin recommended in prevention of cardiac infarction ranges from 75 mg to 325 mg per 24 hours.

The other drug currently used in double anti-platelet therapy is clopidogrel. It belongs to a group of thienopyridine derivatives. Its mechanism of action consists in inhibition of platelets activity through a blockage of adenosine diphosphate (ADP). Combination of clopidogrel and aspirin is more effective in the treatment of patients with severe coronary syndrome, myocardial infarction and patients undergoing coronary reconstructive operation with implantation of stent. Clopidogrel consumption rose significantly from 1997. In 2006 only sale of the drug increased by 12% compared with the year 2005. Yet, in Niteesh's study it was estimated that 56% of patients in the USA use clopidogrel unjustifiably (1).

Prolonged use of acetylsalicylic acid increases the risk of the occurrence of ulceration of stomach or duodenum. In up to 25% of patients ulceration is diagnosed with the use of endoscopy, whereas about 1% suffer from serious complications such as bleeding from ulcer, perforation of the ulcer or bad stomach pain which require hospitalization. The risk of complications connected with the use of ASA is high in patients after 60 years of age. It results from coexisting medical conditions and the application of proper NLPZ family drugs, steroids, anticoagulants and other anti-platelet drugs, e.g. clopidogrel (2).

Research underlines the significance of aspirin dose. Bigger doses (300-325 mg) cause more damage to mucous membrane of the stomach and duodenum than smaller doses (75-100 mg). At the same time it is known that 75 mg dose of ASA inhibits platelets activity for a few days and it doesn't seem that bigger doses are associated with additional benefits (3). An increase in anti-platelet drug dosage does not improve its effectiveness in terms of cardiovascular risk whereas the frequency of complications increases.

Oral antithrombotic drugs (oral anticoagulants – DA) inhibit the coagulation system through blockage of the creation of active coagulant agents. Their action develops slowly and the effectiveness of treatment depends on achieving of so-called therapeutic INR. Application of two anti-platelet drugs and/or oral anticoagulants increases the risk of bleeding into the lumen of alimentary tract upper segment. Patients with triple (ASA + clopidogrel + warfarin) antithrombotic treatment are subjected to a higher risk of bleeding into the lumen of gopp compared with the double therapy (ASA + clopidogrel). It applies to serious bleedings which require transfusion, at least 2 units of concentrated red blood cells, as well as smaller bleedings that require the complement of blood preparations (4). Danish research also proves that the risk of bleeding while applying the combination of ASA/clopidogrel and ASA/oral anticoagulant is few times higher than with the application of a single drug (5).

Bleeding into the lumen of alimentary tract upper segment is burdened with the risk of death. In the overview of writing dealing with mortality in bleedings from gopp attention was paid to a drop in the risk of death within the years 1997-2008 and a rise in the risk of death in a group of patients taking NLPZ and ASA. Mortality amounted to 14.4% before the year 1997 and 20.9% afterwards respectively. On the average mortality among patients taking NLPZ in the discussed period rose by 6.5% (6).

In 2009 in Poland Working Group Consensus on the principles of prophylaxis of gastrointestinal tract complications during anti-platelet treatment was published. Observations of patients prove that groups of higher risk of gastrointestinal complications can be distinguished among people taking anti-platelet drugs. Such groups consist of people with positive ulcer history, elderly people and pa-
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Patients who apply combined therapy (anti-platelet drug and anticoagulant) (7).

The aim of the paper was to analyze the frequency of the occurrence of bleeding into the lumen of alimentary tract upper segment (gopp) in patients taking anti-platelet drugs and oral anticoagulants as well as the assessment of the risk related to the drugs taken.

MATERIAL AND METHODS

Research covered a group of 164 patients hospitalized at the Clinical Department of General Surgery Oncology and Endocrinology of the Provincial Hospital in Kielce over the years 2006-2009. Two subgroups were distinguished out of the whole group: 40 patients taking drugs influencing haemostasis system and 124 patients not taking the above drugs. The patients were admitted to hospital with the initial diagnosis of bleeding into the lumen of alimentary tract upper segment (gopp). The diagnosis was made on the basis of medical history and on physical examination of a patient. Additionally, determination of the erythrocytes number and measurement of hemoglobin and hematocrit concentration were carried out. Indicators of the coagulation system were examined. Conservative therapy was applied in patients at early stage (complementing the volume of vascular bed with crystalloids, colloids or blood derivative preparations, intravenous administration of proton pump inhibitors, intravenous administration of fibrinolyse inhibitors, in specific cases intravenous administration of vitamin K as well as coagulation agents in the form of freshly frozen plasma). Within 24-48 hours endoscopic examination of the alimentary tract upper segment was carried out. During endoscopy mucous membrane of stomach and duodenum was checked. In case of active bleeding therapeutic procedures were applied. The treatment with the use of proton pump inhibitors was given in the form of continuous enema within 72 hours and then oral drugs were used. As quickly as it was possible oral nutrition was included. Detailed assessment covered an average hemoglobin concentration at the admission, average age of patients and mortality rate. The results were subjected to the statistical analysis by the use of the test for comparison of two proportions and the t-Student test for the difference in expected values.

RESULTS

Within the discussed period 164 patients with symptoms of bleeding to the lumen of gopp were treated. Among them there were 94 men (57%) and 70 women (43%). Average age was 61.8 years (from 23 to 91 years). In this group 24.4% (40/164) of patients took drugs influencing coagulation system. This subgroup consisted of patients taking acetylsalicylic acid preparations (ASA), ticlopidine/clopidogrel and/or acenocoumarol. Therapeutic indications for long-term application of drugs were the following: ischemic heart disease, condition after myocardial infarction, auricular fibrillation and condition after implantation of artificial valve of the heart. In the subgroup taking the drugs mentioned above were 21 men (52.5%) and 19 women (47.5%). The average age was 73.6 years (from 48 to 91 years). The patients were significantly older. Among patients taking drugs influencing hemostasis system 23 patients took ASA preparations, ticlopidine/clopidogrel – 5 patients and acenocoumarol – 12 patients. 8 patients took more than one drug, most frequently ASA and ticlopidine/clopidogrel, 1 patient took three drugs. Patients took the drugs for at least 6 months. Average hemoglobin concentration at the admission to hospital among patients taking drugs amounted to 9.09 g/dl.

Majority of patients at the admission were stable in terms of hemodynamic condition. The treatment consisted in complementing the volume of vascular bed, including drugs reducing pH of gastric juice – mainly through the application of proton pump inhibitors, administration of anti-fibrinolytic drugs and in case of taking acenocoumarol applying of freshly frozen plasma and vitamin K. In case when a patient showed clinical symptoms of anemia a concentrate of red blood cells (KKCz) was transfused. According to existing capabilities within 48 hours endoscopic examination of the alimentary tract upper segment in patients was carried out.

Within the whole group of patients hospitalized due to bleeding into the lumen of gopp mortality rate was 9.75% (16/164). In the subgroup of patients taking drugs influencing hemostasis system 6 deaths were reported. Mortality reached 15% (6/40). In the subgroup which did not take drugs it was – 8% (10/124). Among the deceased patients significantly
lower concentration of hemoglobin at the admission can be noticed (average concentration of Hb reached 6.1 g/dl) as well as higher average age of patients (average age of the deceased patients was 77.2 years). All the deceased patients were admitted to hospital with hypovolaemic shock.

Gastroscopic examination which was performed showed: correct picture of gopp in 29 patients, inflammation of mucous membrane of the stomach and/or duodenum in 7 patients and ulceration of the stomach and/or duodenum in 4 patients. Endoscopic interventions based first of all on squirting of ulcer or coagulation were performed in 5 patients.

In the subgroup of patients with symptoms of bleeding taking acenocoumarol average value of INR reached 5.08 (from 1.7 to 18). In this subgroup the basic treatment consisted in adverse results of oral anticoagulant action through the transfusion of FFP. Endoscopic examination did not reveal significant pathologic changes in this group as well.

In total in the whole subgroup 39 units KKCZ and 13 units FFP were transfused. Decisions concerning transfusion were influenced by clinical symptoms and the results of additional examination, i.e. concentration of Hb < 7 g/dl, Ht < 20% and INR > 1.5 together with accompanying features of bleeding into the lumen of alimentary tract.

Statistical analysis

Statistical analysis covered mortality, average hemoglobin concentration and age of patients within subgroups. Results of the assessment of mortality rate are respectively: 0.15 (6/40) in the first subgroup and 0.08 (10/124) in the second one. In order to examine the gravity of differences in mortality rate the test for comparison of two proportions was used. It turned out that there is no sufficient basis for the claim that mortality of patients taking drugs is significantly higher in a statistical sense than average hemoglobin concentration within the group of other patients (value p<0.001). Average age of patients within the deceased group is not significantly higher than average age within the group of other patients (value p=0.133).

DISCUSSION

In meta-analysis of 14 randomized examinations with the use of placebo the risk of severe bleedings within the population taking aspirin in small doses was 2.07 times higher compared with the population taking placebo. Experts estimated that 833 patients have to take aspirin in small doses for one year to have a single episode of severe bleeding into the lumen of alimentary tract reported. Similar results are achieved on observations, though as it was in the case of our study patients with various bleeding risk take part (8).

Endoscopic examination assessing the frequency of the occurrence of mucous membrane ulceration of gopp in patients taking NLPZ did not indicate that it was a risk factor. Higher frequency of erosion occurrence was observed. In our study most frequently significant pathological changes were not found as well. It may result from the fact that endoscopic examination was carried out most often 24-48 hours after the episode of bleeding. The effectiveness of endoscopy in detecting the source of bleeding is the highest within the first 24 hours, and after 72 hours falls to 50% (9).

Patients after the admission to hospital stopped taking anti-platelet drugs, hence topical influence of acetylsalicylic acid was limited. Small doses of aspirin (75-100 mg/d) cause less damage to mucous membrane compared with bigger doses (300-325 mg). Within the discussed group patients used more often Polocard and Acard, which means aspirin in a dose of 75 mg/d.

Well recognized risk factors influence the risk of bleeding into the lumen of alimentary tract. They are, namely: chronic gastric ulcer disease in medical history or past bleeding into the lumen of alimentary tract, simultaneous treatment with the use of oral anticoagulants, other anti-platelet drugs and other NLPZ. Special attention should be paid to the drugs taken by patients. Simultaneous application of anticoagu-
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Lans and ASA as well as NLPZ and ASA drastically increases the risk of bleeding into the lumen of gopp – from 2 to 4 times (3). In our material there were 8 patients (20%). It is estimated that the application of buffered or intestinal preparations ASA does not prevent treatment complications (10). During simultaneous application of anti-platelet drugs and oral anticoagulants possible pharmacological interactions should be taken into consideration. These drugs strengthen the action of DA not changing the value of INR. Hence, it is necessary to inform patients about the risk of treatment (11).

On the assessment examination of the triple therapy (ASA + clopidogrel + warfarin) after the implantation of stent into the coronary vessel it was proved that the application of three drugs significantly increases the risk of bleeding complications. On the other hand discontinuation of drugs application is combined with the risk of thrombosis in stent and as a result with cardiac infarction. Attempts to modify the doses of drugs may bring partial solution to the problem, first of all this refers to a dose of ASA limited to 75 mg/d (4). Among patients under investigation only one person used triple therapy.

Attempts to assess the influence of continuation of anti-platelet treatment with the use of ASA in patients with active bleeding into the lumen of alimentary tract are made. Sung and co. examined a group of 156 patients hospitalized with symptoms of bleeding. In some patients who in spite of that continued to take ASA 2x higher risk of bleeding recurrence within 30 days was reported compared with discontinuation of applying ASA (10.3% vs. 5.4%) (12). In our study we did not dare to continue anti-platelet treatment in case of active bleeding into the lumen of alimentary tract.

Presently the second area for application of aspirin as a prophylactic drug appears. Meta-analysis of examinations covering almost 3000 patients shows that the application of aspirin in a dose of 81-325 mg/d may decrease the risk of adenoma of large intestine development by 6.7%. Advanced forms of adenoma occurred in 12% of patients receiving placebo and in 9% of patients receiving acetylsalicylic acid. In this way the number of patients exposed to undesirable actions of acetylsalicylic acid (13).

The above mentioned Working Group Consensus in case of using anti-platelet drugs suggests the prophylactic application of proton pump inhibitors in cases with ulcer history, past bleeding into the lumen of alimentary tract or applying double anti-platelet treatment and associated anti-platelet and antithrombotic treatment. Prophylactic application of IPP should last as long as it is necessary (7). In surgical treatment anti-platelet drugs and oral anticoagulants may increase the risk of bleeding within perioperative period. The problem was discussed thoroughly by Buksińska-Lisik and Pasierski (14). That is why the risk of bleeding complications during anti-platelet treatment should always be taken into doctor’s consideration while prescribing drugs to a patient. The important thing is to find a balance between benefits and the risk of the applied treatment.

CONCLUSIONS

1. Bleeding into the lumen of alimentary tract upper segment (gopp) is burdened with significant mortality in patients with low hemoglobin concentration and hypotension at the admission to hospital.
2. In patients with bleeding into the lumen of gopp, taking cardiologic drugs influencing the hemostasis system does not increase significantly statistical number of deaths caused by bleeding.
3. During the treatment of bleeding into the lumen of gopp in patients applying drugs mentioned above a compromise between the cardiovascular risk and the risk of death of bleeding should be worked out.

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