

Analysis of the upper gastrointestinal tract bleeding prevalence in patients treated due ischaemic heart disease

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Abstract

Purpose: The analysis concerning the frequency of bleedings from the upper part of the gastrointestinal tract in group of patients suffering from ischaemic heart disease (IHD) treated and not treated with coronaroplasty. The other aim of the study was to analyse the incidence of using particular groups of drugs.

Material and methods: 150 patients were included in the study, aged from 17 to 86. They were divided into three groups: I group – patients treated with coronaroplasty (n=50), II group – patients who were not treated with coronaroplasty (n=50), III control group (n=50). The patients filled in a questionnaire (among other things the questions concerned methods and period of treating heart ischaemia and stomach complaints. The documentation of the keyhole examinations of the upper part of the digestive tract was analysed in flashback).

Results: Bleeding from the upper part of the gastrointestinal tract (only single episode) was noticed in 5 patients (treated with IHD) (3.33%). All these patients belonged to the group II. Endoscopic examination of the upper part of gastrointestinal tract was carried out in 4 of these patients and haemorrhagic gastritis has been found.

The following drugs were more frequently used in patients treated with coronaroplasty: acetylsalicylic acid, clopidogrel, ticlopidine. Acenocoumarol was more frequently used in patients not treated with coronaroplasty. The differences were not significant and concerned the usage frequency of the following drugs: beta-blockers, calcium canal blockers, ACE, systemic nitrates and statins.

Conclusions: Bleeding from the upper part of gastrointestinal tract occurred more frequently among patients not treated with coronaroplasty. The following drugs were used more frequently in the group of patients treated with coronaroplasty: acetylsalicylic acid, ticlopidine and clopidogrel, but acenocoumarol was used more frequently in the group of patients treated only pharmacologically.

Key words: ischaemic heart disease, gastrointestinal bleeding, coronaroplasty.

Introduction

Bleedings from the upper part of gastrointestinal tract are the most popular life-threatening emergencies in gastroenterology. It has been estimated that such complications occur in 1/1000 inhabitants a year [1,2]. The mortality rate due to bleedings from the gastric and duodenal ulcers was 10% [3]. Risk of bleeding concerning patients with chronic peptic ulcer disease, not treated with drug inhibiting hydrochloric acid secretion, was 2-3% [2]. According to other reports, 50% of bleedings from the gastrointestinal tract were caused by chronic peptic ulcer disease [4].

There are the following causes of bleeding from the upper part of gastrointestinal tract: gastric or duodenal ulcer – 30-45%, erosive or haemorrhagic gastritis – 10-20%, oesophageal varices 10-30%, Mallory-Weiss syndrome – 5-15%, non-malignant gastric tumours, blood vessels diseases, malignant gastric tumours, oesophagitis, haemorrhagic diathesis, others (mechanical injuries, aorta-jejunal fistula, stress ulcer) [5].

The majority of bleedings requires endoscopic treatment due to the fact that process of haemostasis is disturbed in the acid environment. After vessel injury, first of all the platelets start to adhere to collagen of the endothelium basement membrane, the platelets aggregate and form the platelet plugs that provide haemostasis for several hours till the fibrin formation. The platelets

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Table 1. The analysis of sex, place of residence, age, weight of patients and period of treating the heart ischaemic disease

Characteristic	Group			Statistical significance	
	I n/%	II n/%	III n/%		
sex	male	40/80	33/66	28/56	p=0.037 (IS)
	female	10/20	17/34	22/44	
place of residence	city	35/70	43/86	42/84	p=0.93 (NS)
	village	15/30	7/14	8/16	
age	medium	62.9	64.1	51.7	p=0.001 (WIS)
	median	61.5	61.5	55	
	minimum	39	47	17	
	maximum	80	82	86	
BMI	medium	26.6	28.3	25.8	p=0.02675 (IS)
	median	27.0	27.9	25.5	
	minimum	18.4	18.3	18.2	
	maximum	39.2	40.4	40.6	
period of treating (months)	medium	58.4	68.6		p=0.5061 (NS)
	median	36	36		
	minimum	1	1		
	maximum	396	312		

aggregation is reduced by half in the pH environment equal to 6.4, but it is abolished in the pH equal to 5.4. There are frequent recurrences in the case of spontaneous bleeding arrest. Pepsin is reactivated at the pH level <4 and as a proteolytic enzyme it initiates clot dissolving [2].

Treatment is divided into an endoscopic and pharmacological one. There are the following endoscopic methods for the treatment of bleeding from the upper part of gastrointestinal tract: the injection methods (using isotonic saline solution, adrenaline, sclerosing agents, agents increasing clotting capability, tissue glues), the thermal methods (electrocoagulation, thermal probe, microwave coagulation, argon laser), the mechanical methods (rubber bands, clips) and the combination of above mentioned methods. Pharmacological treatment includes drugs inhibiting hydrochloric acid secretion in the stomach (proton pump inhibitors) and prostaglandins analogues (i.e. misoprostol) [5].

The following cardiologic drugs are the most frequent cause of bleedings from the gastrointestinal tract:

a) heparin – bleeding is caused by the excessive blockage of fibrin formation and inhibition of proper haemostasis. This symptom depends on the dose, patient haemostatic response, administration method and other factors connected with a patient clinical state. It was stated that the bleeding frequency increases together with the increase of heparin dose and administration method [6]. Heparin can also cause thrombocytopenia and concomitant arterial thrombosis due to the aggregating platelets. This process is supposed to be evoked by immunological complexes IgG-heparin, but venous thrombosis can be a result of heparin neutralisation by the factor 4 that is released from the aggregating platelets during the treatment with this preparation [6];

b) derivative of coumarin – bleeding is caused by a decrease of vitamin K dependent clotting factors. Predisposing factors for bleeding occurrence are also diseases that affect decrease of above mentioned factors (intestinal malabsorption syndrome,

hypermetabolic states, liver damage, alcoholism, renal diseases, haemorrhagic diathesis) and also gastric and duodenal ulcer disease and surgical procedures [6];

c) acetylsalicylic acid – bleeding, beside complications connected with chronic peptic ulcer disease, can be caused by an inhibition of the platelets aggregation and by diminished synthesis of clotting factors VII and IX [7]. Acetylsalicylic acid as an acid substance becomes the non-ionised form in the acid environment, more easily penetrating through the mucus, which passes through phospholipid cell membrane into the much more alkaline inside of the stomach mucosa cells. Acetylsalicylic acid is accumulated there, inhibiting cyclooxygenase 1 (COX1) and by this way inhibiting prostaglandins and prostacyclins production (gastric and duodenal mucosa protective factors) [4].

The aim of the study was to perform the analysis concerning the frequency of bleeding from the upper part of the gastrointestinal tract in the group of patients suffering from ischaemic heart disease (IHD) treated and not treated with coronaroplasty, in comparison with the control group. The other aim of the study was to analyse the incidence of using particular groups of drugs in investigated groups.

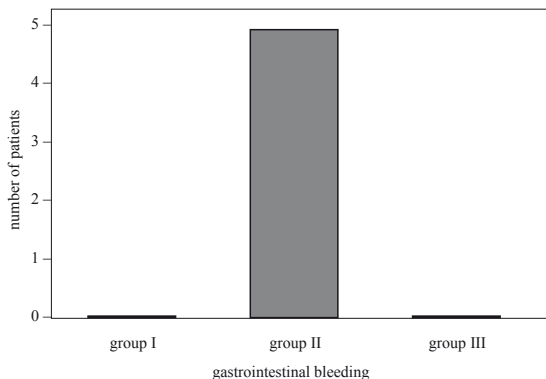
Material and methods

One hundred fifty patients were included into the study, aged from 17 to 86 years. Patients were treated in the Chair and the Department of Cardiology and Internal Diseases of the Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń and in the Clinical Ward of Cardiology and Cardiosurgery of the Military Clinical Hospital No10 in Bydgoszcz.

There were 100 patients with diagnosed IHD and 50 of them belonged to the comparative group with other cardiologic problems (patients treated due to arterial hypertension, arrhythmias, patients diagnosed in a case of fainting or syn-

Table 2. Analysis of bleedings from the upper part of the gastrointestinal tract in particular groups

	Group			Total n/%	group I,II,III p=0.0057 (WIS)	Statistical significance	
	I n/%	II n/%	III n/%			group I and II and also control group III p=0.1078 (NS)	group I and II p=0.0218 (IS)
bleeding from the upper part of the gastrointestinal tract	0/0	5/10	0/0	5/3,33			
Number of treating	50	50	50	150			

Figure 1. Analysis of bleedings from the upper part of the gastrointestinal tract in particular groups

cope). Patients were divided into three groups: I – patients with diagnosed IHD, treated with coronaroplasty and pharmacologically – 50 patients, II – patients with diagnosed IHD, not treated with coronaroplasty but they were treated pharmacologically – 50 patients, III – patients constituting comparative group – 50 patients.

Results were analysed statistically using SAS/Statistica. (The importance of differences between numbers in particular subgroups were verified by means of a test χ^2 on levels $p \leq 0.05$ (IS) and $p \leq 0.01$ (WIS). Due to the expected low numbers the Ystes correction was made and non-parametric variances of the analysis of Kruskal Wallis alternation (age, period of disease). The single-factor analysis of alternation and tests post hoc Sheffe (BMI) [8] were used for the analysis of three groups (I, II, III).

Results

There were 67% of males and 33% of females in the investigated group of 150 patients. Eighty percent of patients lived in the town and 20% lived in the country. The average age in the studied group was 59.6 years (from 17 to 86 years). The average BMI value was 26.9 (from 18.2 to 40.6), but the average duration of treatment on account of ischaemic heart disease was 42.3 months (from 1 to 396 months). Detailed analysis is shown in *Tab. 1*.

Bleeding from the upper part of the gastrointestinal tract, was found in 5/150 patients (3.33%). All bleeding patients belonged to the group II. Endoscopic examination of the upper part of the gastrointestinal tract was performed in 4 patients (one patient did not agree to this examination) and haemorrhagic gastritis was diagnosed.

The statistically higher incidence of bleeding from the upper part of the gastrointestinal tract was proved to occur among patients from group II, comparing all groups ($p=0.0057$), but also group I and II of patients who underwent or not underwent coronaroplasty ($p=0.0218$). Detailed analysis is shown in *Tab. 2* and in *Fig. 1*.

It was proved that the following drugs were statistically more frequently used in patients treated with coronaroplasty: acetylsalicylic acid, clopidogrel, ticlopidine.

Acetylsalicylic acid (ASA) was used in group I in 100% of patients, but in 84% of patients in group II ($p=0.0099$). The reason for renunciation of using ASA among patients from the group II was allergy or this drug as withdrawn in two patients due to chronic peptic ulcer disease.

Clopidogrel was used in 64% of the patients treated with coronaroplasty (in 8% of patients from the group II) ($p=0.000$), but ticlopidine in 56% of those patients (in 28% of patients from the group II) ($p=0.0046$). Acenocoumarol was statistically significantly more frequently used in patients not treated with coronaroplasty – in 20% (in 4% of patients from the group I) ($p=0.0138$). The fibrinolytic treatment was statistically significantly more frequently applied in patients not treated with coronaroplasty – 38%, but in patients treated using invasive methods – 16% ($p=0.0132$).

Some of investigated patients (group I i II) were treated due to ischaemic heart disease up to several years (from 1 to 396 months). During this time some of them suffered from myocardial infarctions, treated with fibrynolysis, independently of the subsequent treatment with coronaroplasty or without coronaroplasty.

The statistically significant differences were not proved, analysing the frequency of applying such drugs as beta-blockers, calcium canal blockers, angiotensin II convertase inhibitors (ACE), systemic nitrates and statins, but beta-blockers were observed to be more frequently used in group II and the remaining drugs were more frequently used in group I ($p > 0.05$). However the difference was not statistically significantly. Detailed analysis is showed in *Tab. 2* and in *Fig. 1*.

Discussion

Ischaemic heart disease (IHD), but particularly myocardial infarction is connected with the necessity for drugs administration for many years. Our own studies revealed bleeding from the upper part of the gastrointestinal tract in 5 patients (treated due to IHD) (5%). All patients belonged to the group II. Endoscopic examination was performed in 4 patients (one patient did not agree to be examined) and haemorrhagic gastritis was

Table 3. Analysis concerning the incidence of particular drugs groups application in patients treated (group I) and not treated with coronaroplasty (group II)

Drugs group	Group		Total n/%	Statistical significance
	I n/%	II n/%		
acetylsalicylic acid	50/100	42/84	92/92	p=0.0099 (WIS)
clopidogrel	32/64	4/8	36/36	p=0.0000 (WIS)
ticlopidine	28/56	14/28	42/42	p=0.0046 (WIS)
acenocoumarol	2/4	10/20	12/12	p=0.0138 (IS)
beta-blocker	36/72	41/82	77/77	p=0.2346 (NS)
Ca-canal blocker	7/14	3/6	10/10	p=0.3173 (NS)
ACE inhibitor	45/90	39/78	84/84	p=0.1017 (NS)
nitroglycerin	12/24	11/22	23/23	p=0.8122 (NS)
statins	34/68	28/56	62/62	p=0.2164 (NS)
streptokinase and/or heparin	8/16	19/38	27/27	p=0.0132 (IS)
number of patients	50	50	100	

stated. Our own studies also proved that drugs as acetylsalicylic acid, clopidogrel, ticlopidine, were statistically significantly more frequently used in patients treated with coronaroplasty. Acetylsalicylic acid was used in group I in 100% of patients, but in 84% of patients in group II.

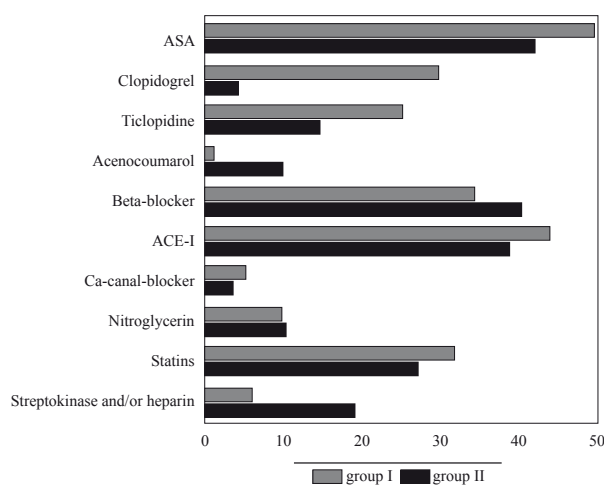
Our results are in accordance with other authors' reports. According to Jayaprakash et al. [9], 90% of patients suffering from ischaemic heart disease have taken aspirin.

Six percent of patients from our studied group were forced to stop treatment with acetylsalicylic acid (allergy or chronic peptic ulcer disease).

According to Reguła et al. [10], the necessity for interruption of ASA treatment due to gastrointestinal complications was 14.5% and 12% according to McCarthy [11].

Bleedings from the upper part of the gastrointestinal tract are described in the literature to occur most frequently after non-steroidal anti-inflammatory drugs, including aspirin. Singh et al. [12] report that it occurs in 1-4%, according to Serrano et al. [13] – in 4.5%, according to Ibanez et al. [14] – in 4.0%. In accordance with Laine [15], gastrointestinal complications caused by non-steroidal anti-inflammatory drugs application, appear in 3-4.5% including severe complications like bleeding, perforations and death – in 1.5%. According to He et al. [16] aspirin increases twice the probability of bleeding from the gastrointestinal tract. Other reports concerning aspirin inform about gastrointestinal tract complications of patients suffering from ischaemic heart disease comparing with patients not suffering from this disease. In accordance with Bar-Dayyan et al. [17], bleeding from the gastrointestinal tract is more frequent in patients who apply anticoagulative drugs. Serrano et al. [13] also more frequently observed bleeding from the upper part of the gastrointestinal tract in patients with ischaemic heart disease.

Other authors claim that the main reason for gastrointestinal bleedings are non-steroidal anti-inflammatory drugs that constitute 20-30% of gastrointestinal bleedings according to Muszyński et al. [18], 52% according to Loginov et al. [19] and 40% according to Langman [20]. In accordance with Krasowski [5], erosive or haemorrhagic gastritis after applying non-steroidal anti-inflammatory drugs, is the reason for

Figure 2. Analysis concerning incidence of particular drugs groups application in patients treated and not treated with coronaroplasty

10-20% of bleedings. Sapoznikov et al. [21] proved that among 318 patients suffering from gastrointestinal bleeding, 28% of them have been using aspirin for 30 days.

Our own studies revealed described bleedings as single incidents. There are a lot studies in the literature concerning gastrointestinal bleedings recurrence in patients treated with non-steroidal anti-inflammatory drugs. Laine et al. [22] stated probability of repeated bleeding in 4% of patients.

Other studies concern gastrointestinal bleedings caused by other remaining antiplatelet drugs. In accordance with Schamig et al. [10], ticlopidine significantly decreases the risk of haemorrhagic complications in comparison with other anticoagulants. Meissner et al. [23] observed 84 patients treated due to myocardial infarction and he found bleedings after streptokinase in 10 cases – 12%, including 5-6% of deaths (there were central nervous system bleedings in 3 cases, retroperitoneal haemorrhage in one case and one haemorrhage from the wound) in remaining 5 patients. The next 3 cases of bleeding included intramuscular bleedings, 1 case of bleeding from duodenal ulcer and 1 case of spontaneous rupture of the spleen.

According to Landefeld et al. [24], patients who use oral anticoagulants for three years will develop gastrointestinal bleeding. In accordance with Solet et al. [25], gastrointestinal bleedings occur 2.5 times less frequently after ticlopidine and clopidogrel than after aspirin, but application of these two groups of drugs causes three times as large increase of bleedings amount. Ibanez et al. [14] observed gastrointestinal bleedings after clopidogrel in 2.3% of patients, but after ticlopidine in 3.1% of patients. According to Ng et al. [26], clopidogrel is connected with the increased risk of gastrointestinal bleeding.

During our study, bleedings in other systems and organs were not observed in the respondents. Haemorrhagic complications in other systems during the treatment with anti-aggregative drugs were described among others by McKevitt et al. [27], who noted bleedings into the central nervous system after clopidogrel in 9%, after heparin in 17%. Cay et al. [28] described bleedings into the central nervous system after clopidogrel. Bleedings into the lungs after clopidogrel and receptor IIb/IIIa inhibitors were described by Gill et al. [29]. According to Yusuf et al. [30], severe bleedings – it means bleedings that cause significant disability, loss of vision after blood effusions into the eye or bleedings requiring transfusion of 2 blood units – in patients using both clopidogrel and acetylsalicylic acid occur with the incidence of 3.7%. In accordance with Jones et al. [31], there were no differences concerning haemorrhagic complications in patients using acetylsalicylic acid or clopidogrel, but these complications occur more frequently in patients who apply these two drugs at the same time. Andryś et al. [6] described the internal programme concerning notification of side effects during applied therapy in the Department of Clinical Pharmacology of Medical University of Poznań. This programme was based on observations in the hospital departments of State Clinical Hospital No 1 of Medical University of Poznań during the years 1991-1994. The suspicion about side effects during the antithrombotic therapy was notified in 18 patients. Bleedings from the gastrointestinal tract after treatment with heparin were observed in 1 patient, bleedings from urinary tracts or genital tracts in 2 patients and 2 patients revealed duodenal bleeding proved in endoscopy.

It is plausible to formulate the following conclusions on the basis of the research carried out:

1. Bleeding from the upper part of gastrointestinal tract more frequently occurred among patients not treated with coronaroplasty,
2. The following drugs were more frequently used in the group of patients treated with coronaroplasty: acetylsalicylic acid, ticlopidine and clopidogrel, but acenocoumarol was used more frequently in the group of patients treated only pharmacologically.

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