

Risk factors for colonic diverticular bleeding: A Westernized community based hospital study

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Author contributions: Jansen A collected the data and interpreted the literature; Harenberg S performed the statistics; Grenda U did part of the literature research; Elsing C interpreted the clinical data, and conceived and wrote the manuscript.

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CONCLUSION: Beside nonsteroidal anti-inflammatory steroid drug use, antihypertensive medication and concomitant arteriosclerotic diseases are risk factors for colonic diverticular hemorrhage. Our results support the hypothesis of an altered arteriosclerotic vessel as the source of bleeding.

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Key words: Diverticula; Gastrointestinal bleeding; Arteriosclerosis; Risk factors; Calcium channel blocker

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Abstract

AIM: To evaluate the risk factors-other than nonsteroidal anti-inflammatory drugs-for colonic diverticular bleeding in a westernized population.

METHODS: One hundred and forty patients, treated for symptomatic diverticular disease in a community based hospital, were included. Thirty (21%) had signs of diverticular bleeding. Age, gender, and the results of colonoscopy were collected and compared to a group of patients with nonbleeding symptomatic diverticulosis. Records were reviewed for comorbidities, such as obesity, alcohol consumption, smoking habits and metabolic diseases. Special emphasis was put on arterial hypertension, cardiovascular events, diabetes mellitus, hyperuricemia and hypercholesterinemia.

RESULTS: There was no difference between patients with diverticular hemorrhage and those with nonbleeding symptomatic diverticulosis regarding gender ratio (male/female 9/21 vs 47/63) and diverticular localisation. Bleeding patients differed in respect to age (73.4 ± 9.9 vs 67.8 ± 13.0 , $P < 0.013$). Significant differences were found between both groups regarding the presence of hyperuricemia and use of steroids and nonsteroidal anti-inflammatory drugs. Patients with three concomitant metabolic diseases were also identified as being at risk of bleeding. A forward stepwise logistic regression analysis revealed steroids, hyperuricemia and the use of calcium-channel blockers as independent risk factors of bleeding.

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INTRODUCTION

Diverticular disease is common in Westernized countries^[1]. In adults under 40, less than 10% are affected. This increases to a prevalence of up to 60% in those aged over 80. Prevalence is equal between men and women. In Western countries the disease usually affects the left side of the colon^[2], whereas in Eastern countries diverticulosis is more common in the right side^[3]. In 80% of affected individuals, the condition remains asymptomatic. The remaining patients develop signs of diverticular disease. These include left sided lower abdominal pain, change in bowel habits and abdominal distension. Complicated diverticular disease presents as diverticulitis with perforation, obstruction, formation of abscesses and fistulation^[4]. The second severe complication is the acute diverticular bleeding, which affects 3% to 15% of individuals with diverticular disease^[5,6]. The pathogenesis of diverticular bleeding includes an asymmetric intimal proliferation and segmental weakening of the associated vas rectum arising from traumatic factors within the diverticular or colonic lumen. The bleeding is thought to be the

result of an acute rupture of the altered vasa recta close to the diverticulum^[7]. Arteriosclerosis and associated diseases such as the metabolic syndrome could therefore play an important role in the pathogenesis of acute diverticular bleeding. Nonsteroidal anti-inflammatory drugs (NSAID), including aspirin, have already been identified as risk factors for acute lower gastrointestinal bleeding, including acute diverticular bleeding^[3,8-10]. In a recently published survey, several potential risk factors for diverticular bleeding have been analysed in Japanese patients. Apart from NSAID and anticoagulants, arterial hypertension has been shown to be an independent risk factor for colonic diverticular bleeding^[3]. Risk factors for diverticular bleeding in Western populations have not been explored before. We therefore analysed patients admitted to a Western community based hospital with colonic diverticular bleeding regarding comorbidities and medications as possible risk factors.

MATERIALS AND METHODS

Two hundred and one patients, treated for symptomatic diverticular disease at the medical Department of the St. Elisabeth Hospital, Dorsten, between January 2004 and July 2006, were included in this study. Overall, 140 patients with proven diverticulosis and colonoscopy during the hospital stay were reviewed retrospectively. The remaining patients either refused endoscopy or went directly to surgical intervention. None of the latter patients suffered from intestinal bleeding.

Thirty of the 140 investigated patients had signs of lower intestinal bleeding on admission. Data from these patients was compared to data from patients without signs of lower gastrointestinal bleeding.

Data collection

We collected data on age, gender and results of colonoscopy. The records were also reviewed for information on comorbidities, ongoing medication, body mass index (BMI), alcohol consumption and smoking habits. Special emphasis was put on concomitant diseases such as arterial hypertension, cardiovascular events (stroke, coronary heart disease), diabetes mellitus including prediabetes (impaired glucose utilization), hyperuricemia and hypercholesterolemia. In addition, outcome, development of complications and length of hospital stay were compared. Concomitant diseases were assumed when patients were on appropriate medication. Obesity was defined as BMI > 25 kg/m².

Colonoscopy

Colonoscopy was performed after using polyethylene glycol-containing lavage solution for colon preparation by use of electronic video endoscopes (Model Exera CF-Q 145/160, Olympus Optical Co, Hamburg, Germany). Diagnosis of colonic diverticular hemorrhage was made based on the criteria reported by Jensen *et al*^[6]. These criteria include the observation of active bleeding from a diverticulum, the observation of blood clots

Table 1 Characteristics of patients with and without colonic diverticular hemorrhage *n* (%)

	Diverticular hemorrhage	Nonbleeding diverticular	<i>P</i> value
No	30	110	
Age (yr, mean ± SD, range)	73.4 ± 9.9 (50-90)	67.8 ± 13.0 (40-93)	0.013
Male/Female ratio	9/21	47/63	NS
Diverticular location			
Left side	22 (73.3)	84 (77.8)	NS
Bilateral	8 (26.7)	24 (22.2)	

Data are mean ± SD; NS: Non significant.

in the colon in the presence of diverticula, absence of blood in the terminal ileum, and no other demonstrable cause of bleeding.

Statistical analysis

The data were evaluated using descriptive statistical methods (mean ± SD, ranges). For comparison of two means the unpaired Student's *t*-test was used. Frequency distribution was calculated by the χ^2 test or Fisher's exact probability test. Factors with *P* < 0.2 in the univariate analysis were included in a forward stepwise logistic multivariate regression analysis. Statistical calculations were performed using SPSS Version 16.0 for Windows (SPSS Inc Chicago, USA).

RESULTS

The characteristics of patients with and without colonic diverticular hemorrhage are shown in Table 1. While gender distribution was comparable, patients with diverticular bleeding were significantly older. None of our patients had isolated right-sided colonic diverticula. Isolated left-sided colonic affection was most frequent in both groups.

Colonoscopy was performed in the bleeding group after 3.8 ± 2.3 d (range 1-9) and in the nonbleeding group after 6.0 ± 3.7 d (range 1-28, *P* = 0.003). Colonoscopy was successful in 83% of bleeding patients and in 79% of nonbleeding patients. The reasons for early termination were obstruction in 10% of patients in the bleeding group and 17% in the nonbleeding group. In the remaining patients colonoscopy was incomplete because of inappropriate cleaning or pain.

Endoscopic signs of diverticular inflammation (petechial bleeding, pus, reddening, and swelling) were found in 63.3% of patients in the bleeding group and 59.1% of patients in the nonbleeding group (NS).

Since polyps are also potential sources of bleeding we compared the prevalence of such lesions in both groups. In the bleeding group polyps were found in seven patients (23%) whereas, in the nonbleeding group, 29 patients (26%, NS) had polyps. None of the polyps showed signs of recent hemorrhage.

The definitive source of bleeding was identified in nine (30%) patients (bleeding vessels, nonbleeding

Table 2 Potential risk factors for diverticular bleeding *n* (%)

	Diverticular hemorrhage	Nonbleeding diverticular	<i>P</i> value
No	30	110	
Comorbidities			
BMI (kg/m ² , mean ± SD, range)	28.2 ± 5.0 (21-43)	26.7 ± 5.0 (13-46)	0.15
Obesity (BMI > 25 kg/m ²)	20 (69.0)	61 (59.2)	0.34
Diabetes mellitus	7 (23.3)	15 (13.6)	0.2
Hypertension	20 (66.7)	65 (59)	0.45
Hyperlipoproteinemia	8 (26.7)	25 (22.7)	0.65
Hyperuricemia	6 (20)	8 (7.3)	0.039
Smoking	2 (6.7)	17 (15.5)	0.21
Alcohol	0	5 (4.6)	0.23
Immunodeficiency ¹	4 (13.3)	9 (8.2)	0.39
Cardiovascular events ²	10 (33.3)	28 (25.5)	0.39
Medication			
Steroids	4 (13.3)	3 (2.7)	0.018
NSAR	4 (13.3)	4 (3.6)	0.043
Cumarine	2 (6.7)	4 (3.6)	0.47
Aspirin	9 (30.0)	30 (27.3)	0.77
β-blockers	7 (23.3)	33 (30.0)	0.47
ACE-inhibitors	6 (20.0)	25 (22.7)	0.75
AT-II-receptor-antagonists	0	10 (9.1)	0.087
Calcium antagonist	10 (33.3)	23 (20.9)	0.15
Digitalis	5 (16.7)	7 (6.4)	0.074

¹Including malignant disease, chemotherapy, regular intake of methotrexate or steroids, reduced general condition due to old age.

²Including stroke and myocardial infarction.

vessel in the diverticulum and adherent clot in the diverticulum). The bleeding was localized in the right colon in one patient and in the left colon in the remaining patients. Colonoscopy was performed with these patients within three days (1.8 ± 0.7 d), whereas patients without definitive signs of bleeding were examined between day two and nine after admission (4.7 ± 2.2 , $P < 0.001$).

To identify potential risk factors for diverticular bleeding we compared bleeding and nonbleeding patients regarding comorbidities and medications. The results are shown in Table 2. Hyperuricemia was present significantly more often in patients with diverticular bleeding. All other comorbidities showed no significant differences. However, patients were more likely to develop diverticular bleeding when more than three concomitant diseases, out of seven (obesity, hypertension, hypercholesterolemia, hyperuricemia, impaired glucose utilization, arteriosclerosis, immunosuppression), were present ($P = 0.013$). By univariate analysis, steroid and NSAID use were also increased in patients with bleeding. In addition, diabetes mellitus, BMI, calcium channel blockers and digitalis had a P value < 0.2 . Using these factors, we performed a multivariate forward logistic regression analysis: steroid use ($P = 0.01$), hyperuricemia ($P = 0.004$), and use of calcium channel blockers ($P = 0.03$) were confirmed independent factors of bleeding.

There was no difference in length of hospital stay between the bleeding and the nonbleeding group. During hospital stay, four patients from the bleeding group (13.3%) and eight from the nonbleeding group

(7.3%, $P = \text{NS}$) required surgery.

Severity of diverticular hemorrhage was classified according to the initial RBC in 28 patients. Patients with an initial hemoglobin level lower than 10 g/dL were considered to have more severe bleeding. These patients were older than those with a less severe bleeding (81 ± 4 vs 72 ± 10 years, $P = 0.037$). All other potential risk factors showed no differential distribution between the groups, although trends could be seen in steroid use, NSAID use and cardiovascular events.

Length of hospital stay differed between severe and non-severe bleeding patients (17 ± 10 d vs 10 ± 7 d, $P = 0.067$). Two patients in the severe group died due to cardiovascular events and multiple organ failure. No patient of the non-severe group died.

DISCUSSION

Our study shows that the risk of diverticular bleeding increases with age. In particular, higher age is associated with a more severe bleeding. Steroid and NSAID use predisposes to diverticular bleeding. Hyperuricemia, steroid and calcium channel blockers use are independent risk factors for bleeding out of a variety of atherosclerotic diseases and medications. A higher bleeding risk is also associated with the concomitant presence of more than three of such conditions.

The prevalence of diverticular disease, in general, increases with age^[5]. Complicated diverticulitis, including obstruction, perforation and abscess formation leading to operation, however, is more likely in patients younger than 50 years of age with coexisting conditions, including obesity^[11]. Our results show that in contrast diverticular bleeding is an event which occurs in older age. In addition, obesity has no influence. The association of obesity and diverticular disease is controversial. A slight association between elevated BMI and symptomatic diverticular disease was reported by Aldoori *et al*^[12], whereas other authors did not find such a correlation^[13,14]. In our study the prevalence of obesity in the bleeding and nonbleeding group was comparable to the reported prevalence of obesity in the general population of this urban area^[15]. Thus, the presence of diverticula and the occurrence of a bleeding episode are both independent of obesity.

Diverticular bleeding and complicated diverticular disease are of different pathogenesis. This is supported by our observation that patients with bleeding had no higher frequency of inflammation than patients without bleeding^[16]. Diverticular bleeding is thought to be the result of a rupture of an arteriosclerotic altered diverticular vessel^[7,17]. Since arteriosclerosis increases with age, age itself might not be an independent risk factor for bleeding^[13]. Instead, arteriosclerotic disease could be the true risk factor for bleeding. In our study, we could not find an association of bleeding with a single arteriosclerotic disease. Arteriosclerosis is also the result of different metabolic diseases. Therefore we speculate that the presence of these diseases increases

the risk of bleeding. Our results show that this is only true for hyperuricemia, but not for other metabolic diseases, including obesity. A recent survey on Japanese patients confirms our results, that arteriosclerosis in general and obesity are not single independent risk factors for bleeding. However, these authors identified arterial hypertension as the only independent risk factor for hemorrhage^[3]. Although in our study arterial hypertension is not associated with a higher bleeding risk, hyperuricemia is. Yamada *et al*^[3] speculate from their findings that microscopic hemorrhages occur frequently in diverticulosis and progress into severe bleeding in the presence of unfavorable conditions, such as arterial hypertension. This speculation is supported by the finding that NSAID use, by causing microscopic bleeding, also increases the risk of significant diverticular bleeding.

From our results we can conclude that, beside arterial hypertension and NSAID use, additional conditions, like hyperuricemia and steroid use, are additional risk factors of bleeding. Furthermore, the combination of several arteriosclerotic risk factors is also associated with a higher bleeding risk. This supports the hypothesis that vascular fragility is increased in elderly patients, and especially in patients with multiple concomitant diseases. NSAIDs reduce mucosal prostaglandin production, which leads to enhanced mucosal permeability and reduced microcirculation, and, in turns, to mucosal inflammation and bleeding^[18,19].

In our study, hyperuricemia was a risk factor for diverticular bleeding. This fits into the concept that metabolic diseases leading to arteriosclerosis could cause the bleeding episode. And indeed, uric acid has been identified as a risk factor for stroke and myocardial infarction^[20]. In our study, hyperuricemia was assumed when patients were on adequate medication (allopurinol). Thus we cannot exclude that allopurinol itself could have an influence on diverticular bleeding. Calcium channel blockers use was also associated with a higher bleeding risk. An elevated risk for gastrointestinal bleeding is known to be present in older adults following calcium channel blocker use^[21,22]. Thus, our observation shows that diverticula are a possible source of bleeding in these patients. Therefore, it should be kept in mind that older patients with arterial hypertension and diverticula have an elevated risk for gastrointestinal bleeding when treated with calcium channel blockers.

In our study, most patients suffered from left sided diverticular disease. Accordingly, this was also the most frequent localisation of the bleeding diverticulum. This is in contrast to the general opinion where right sided diverticula are thought to be the most frequent source of bleeding. However there are only limited data which support this hypothesis. Even a recent Japanese study could not find such an association^[3].

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COMMENTS

Background

Diverticular disease of the colon is common in Westernized countries. One of its complications is bleeding. Our study tried to identify the risk factors for this event.

Research frontiers

To know potential risk factors for bleeding is essential for treating patients with diverticulosis and concomitant diseases.

Innovations and breakthroughs

In Westernized countries, the risk factors for diverticular bleeding are the use of nonsteroidal anti-inflammatory drugs (NSAID), the use of steroids, antihypertensive medications and concomitant arteriosclerotic diseases. Anticoagulation and antiplatelet therapies were not identified as risk factors.

Applications

Patients with known diverticula should avoid NSAID, and during antihypertensive medication the risk for diverticula bleeding should be kept in mind.

Terminology

Diverticula are herniations of the mucosa and submucosa through the muscular coat of the colon. There is a close relationship between the herniated sac and the arterial supply. This is of importance for the pathophysiology of bleeding.

Peer review

It is a well written paper, substantiating evidence for some known risk factors and identifying some new, like hyperuricemia, and use of calcium channel blocker.

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