

Impact of antiplatelet treatment on colorectal cancer staging characteristics

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Abstract

AIM: To evaluate whether antiplatelet medication leads to an earlier stage colorectal cancer (CRC) diagnosis.

METHODS: From January 2002 until March 2010, patients that presented to our institution with the initial diagnosis of CRC and were submitted to an open curative CRC resection or a palliative procedure were retrospectively reviewed. Exclusion criteria were the use of antithrombotic medication, i.e., coumarins, and appendiceal malignancies. Data acquired from medical files included age, gender, past medical history, antithrombotic treatment received prior to endoscopic diagnosis, preoperative imaging staging, location of the tumor, surgical and final histopathological report. Patients that did not receive any antithrombotic medication prior to the endoscopic diagnosis comprised the control group of the study, while patients that were on antiplatelet medication comprised the antiplatelet group. Primary end point was a comparison of CRC stage in the two groups of the study. CRC presenting symptoms and the

incidence of each cancer stage in the two groups were also evaluated.

RESULTS: A total of 387 patients with the diagnosis of CRC were submitted to our department for further surgical treatment. Ninety-eight patients (25.32%), with a median age of 71 years (range 52-91 years), were included in the antiplatelet group, while 289 (74.67%) patients, with a median age of 67 years (range 41-90 years), were not in any thrombosis prophylaxis medication (control group). Thirty-one patients were treated with some kind of palliative procedure, either endoscopic, such as endoscopic stent placement, or surgical, such as de-compressive colostomy or deviation. Coronary disease (77.55% - 76 patients), stroke recurrence prevention (14.28% - 14 patients) and peripheral arterial disease (8.16% - 8 patients) were the indications for the administration of antiplatelet treatment (aspirin, clopidogrel, ticlopidine or dipyridamole) in the antiplatelet group. All patients on aspirin treatment received a dosage of 100 mg/d, while the minimum prophylactic dosages were also used for the rest of the antiplatelet drugs. Investigation of an iron deficiency anemia (147 patients), per rectum blood loss (84 patients), bowel obstruction and/or perforation (81 patients), bowel habits alterations (32 patients), non-specific symptoms, such as weight loss, intermittent abdominal pain and fatigue, (22 patients) or population screening (21 patients) were the indications for the endoscopic investigation in both groups. Bleeding, either chronic presenting as anemia or acute was significantly higher ($P = 0.002$) for the antiplatelet arm of the study (71 patients - 72.4% of the antiplatelet group vs 160 patients - 55.3% of the control group). The mean tumor, node and metastasis stage was 2.57 ± 0.96 for the control group, 2.27 ± 0.93 for the antiplatelet group ($P = 0.007$) and 2.19 ± 0.92 for the subgroup of patients taking aspirin ($P = 0.003$). The incidence of advanced disease (stage IV) was lower for the antiplatelet group of the study ($P = 0.033$).

CONCLUSION: The adverse effect of bleeding that is justifiably attached to this drug category seems to have a favorable impact on the staging characteristics of CRC.

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Key words: Colorectal cancer; Antiplatelets; Cancer stage; Abdominal surgery; Colonoscopy

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INTRODUCTION

Antiplatelet drugs, such as aspirin, dipyridamole, clopidogrel and ticlopidine, are increasingly used in order to prevent cardiovascular events^[1]. Generally, aspirin and the other antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation, especially in the arterial circulation. In high risk patients, even dual antithrombotic therapy is warranted. Prevention of recurrent cardiac ischemia after coronary intervention or by-pass surgery for peripheral arterial disease represents indications where the concurrent administration of two antiplatelet agents increase the prophylactic benefits for the patient^[2]. However, one common side effect of this drug category is the susceptibility to bleeding^[3].

On the other hand, lower gastrointestinal bleeding, either chronic or acute, may be the presenting symptom of colorectal cancer (CRC) that usually dictates the endoscopic work-up. In this retrospective study, we aimed to evaluate whether antiplatelet treatment, a popular medication among elderly patients with concomitant coronary or peripheral arterial disease, leads to an earlier stage diagnosis of CRC. Mean CRC stage in patients receiving antiplatelet medication (antiplatelet group) was compared with CRC stage in their counterparts that were not on any thrombosis prophylaxis medication (control group). CRC presenting symptoms that led to the endoscopic diagnosis and the incidence of each cancer stage in the two groups of the study were also evaluated.

MATERIALS AND METHODS

Internal board approval and ethics committee permission were obtained for the initiation of this study. From January 2002 until March 2010, patients that presented to our institution with the initial diagnosis of CRC and were

submitted to an open curative CRC resection or to a palliative procedure were retrospectively reviewed. Exclusion criteria were: (1) the use of antithrombotic medication, i.e., coumarins; and (2) appendiceal malignancies. Data acquired from the medical files included age, gender, past medical history, antithrombotic treatment received prior to endoscopic diagnosis, preoperative imaging staging, location of the tumor, surgical and final histopathological report.

All patients were staged using the tumor, node and metastasis (TNM) staging system of the American Joint Committee on Cancer. Each TNM cancer stage (I, II, III, IV stage) was signed with a consecutive number (1, 2, 3 and 4 respectively) for comparison purposes. Patients were divided into two groups. Those patients that did not receive any antithrombotic medication (including antiplatelets and coumarins) prior to the endoscopic diagnosis comprised the control group of the study while CRC patients that were on antiplatelet medication comprised the antiplatelet group.

Statistical analysis

The statistical analysis was made using the Statistical Package for Social Sciences version 15 statistical analysis software. In each group, we calculated the TNM cancer stage mean \pm SD. We also assessed the distribution of CRC presenting symptoms and the incidence of each cancer stage in the two groups. The unpaired *t* test was used to compare the mean cancer stage (mean \pm SD) between the two groups while the Fisher's exact test was used to compare the differences in the presenting symptoms and cancer stage incidence.

RESULTS

A total of 387 patients with the diagnosis of CRC were submitted to our department for further surgical treatment. Ninety-eight patients (25.32%), with a median age of 71 years (range 52-91 years), were included in the antiplatelet group, while 289 patients (74.67%), with a median age of 67 years (range 41-90 years), were not on any thrombosis prophylaxis medication (control group). Thirty-one patients (eight patients from the antiplatelet group and twenty-three patients from the control group) were treated with some sort of palliative procedure, either endoscopic (seven patients), such as endoscopic stent placement, or surgical (twenty-four patients), such as de-compressive colostomy or deviation. Advanced loco-regional or metastatic disease and diminished cardiopulmonary resources mandated the utilization of minimally invasive procedures in these patients. We used available data from the preoperative imaging studies and the surgical reports in order to stage these patients.

Coronary disease (77.55% - 76 patients), stroke recurrence prevention (14.28% - 14 patients) and peripheral arterial disease (8.16% - 8 patients) were the indications for the antiplatelet treatment in the antiplatelet group. Aspirin, clopidogrel, ticlopidid and dipyridamole

Table 1 Number of patients in each group of the study (control - antiplatelet group), the type of therapy, tumor, nodes and metastasis stage (1-4) in each group *n* (%)

	No. of patients	TNM stage (mean \pm SD)
Total	387	
Control group	289 (74.6)	2.57 \pm 0.96
Antiplatelet group	98 (25.4)	2.27 \pm 0.93
Aspirin	65	2.19 \pm 0.92
Clopidogrel	17	
Ticlopidid	6	
Dipyridamole	4	
Dual therapy	6	

TNM: Tumor, nodes and metastasis staging system of the American Joint Committee on Cancer.

Table 2 Incidence of colorectal cancer presenting symptoms and the distribution of cancer in the two groups of the study *n* (%)

	Antiplatelet group (<i>n</i> = 98)	Control group (<i>n</i> = 289)
Symptoms		
Anemia	43 (43.8)	104 (35.9)
Blood loss per rectum	28 (28.5)	56 (19.3)
Obstruction/perforation	15 (15.3)	66 (22.8)
Altered bowel habits	3 (3)	29 (10)
Non-specific symptoms	4 (4)	18 (6.2)
Screening	5 (5.1)	16 (5.5)
Distribution		
Right	42 (42.8)	116 (40.1)
Left	33 (33.6)	104 (35.9)
Rectum	23 (23.4)	69 (23.8)

were the antiplatelet agents administered in this patient group (Table 1). All patients on aspirin treatment, mean duration of administration 15.3 \pm 6.51 years, received a dosage of 100 mg/d, while the minimum prophylactic dosages were also used for the rest of the antiplatelet drugs, mean duration of administration 5.85 \pm 3.46 years (Ticlopidid 250 mg twice daily; clopidogrel 75 mg/d; and dipyridamole 200 mg twice daily). Generally, the overwhelming majority of patients reported absolute compliance to the prescribed antiplatelet medication. Only three patients admitted inattentiveness to medication. Regarding dual therapies, four patients were on concurrent aspirin and clopidogrel medication, while in two patients, aspirin was combined with ticlopidid. In addition, twenty-one female patients (six from the antiplatelet group and fifteen from the control group) routinely received calcium supplementation orally. None of the patients in the study received folic acid on a regular basis.

Investigation of an iron deficiency anemia (37.9% - 147 patients), per rectum blood loss (21.7% - 84 patients), bowel obstruction and/or perforation (20.9% - 81 patients), bowel habits alterations (8.2% - 32 patients), non-specific symptoms, such as weight loss, intermittent abdominal pain and fatigue, (5.6% - 22 patients) or population screening (5.4% - 21 patients) were the indications for the

Table 3 The incidence of each stage in each group (Antiplatelet and control group) and the comparison between the two groups *n* (%)

	Antiplatelet group (<i>n</i> = 98)	Control group (<i>n</i> = 289)	<i>P</i> value
Stage I (1)	24 (24.4)	47 (16.2)	0.0721
Stage II (2)	32 (32.6)	79 (27.3)	0.3656
Stage III (3)	34 (34.6)	114 (39.3)	0.4707
Stage IV (4)	8 (8.1)	49 (16.9)	0.033

endoscopic investigation in both groups (Table 2). Although some patients reported more than one symptom, we included the primary indication for the endoscopy in the analysis as it was noted in the colonoscopy report. In cases where the indications overlapped, such as anemia and blood loss per rectum, the initial symptom was only scored. The distribution of CRC (right colon, left colon, rectum) in the two groups is shown in Table 2.

Bleeding, either chronic presenting as anemia or acute, was significantly higher (*P* = 0.002) for the antiplatelet arm of the study (71 patients - 72.4% of the antiplatelet group *vs* 160 patients - 55.3% of the control group) (Table 2). The mean TNM stage was 2.57 \pm 0.96 for the control group, 2.27 \pm 0.93 for the antiplatelet group (*P* = 0.007) and 2.19 \pm 0.92 for the subgroup of patients taking aspirin (*P* = 0.003) (Table 1). Cancer stage incidence in the two groups of the study and the subsequent statistical comparison are shown in Table 3. The incidence of advanced disease (stage IV) was lower for the antiplatelet group of the study (*P* = 0.033).

DISCUSSION

Aspirin, also called acetylsalicylic acid, has become a very popular medication, especially among the elderly. As a platelet aggregation inhibitor, it is used for a variety of medical conditions^[4]. Besides aspirin, newly introduced antiplatelet agents, such as clopidogrel, are also used in order to reduce the risk of thrombosis recurrence in patients with prior myocardial infarction, stroke or peripheral arterial disease^[2,3]. In addition, the beneficial role of non-steroid anti-inflammatory drugs (NSAIDs) seems to also be expanded in the field of primary prevention of CRC. It is suggested that the cyclooxygenase-2 inhibitors and the NSAIDs generally can reduce the risk of colonic adenomas and subsequently the incidence of CRC^[6-9].

However, there is a scarcity of data in the literature regarding the possible favorable effects of antiplatelet treatment on unmasking an existent CRC, leading to an early diagnosis. A study that tried to investigate the characteristics of colon cancer diagnosed in patients taking aspirin or warfarin concluded that bleeding related to aspirin or warfarin use has no effect on an earlier diagnosis of CRC^[10]. In an attempt to throw some additional light on this, we conducted our survey, taking into account, not only aspirin, but also the most recently used antiplatelet agents. However, we avoided including coumarins in

our analysis as the final antithrombotic effect in this drug category is determined by the international normalized ratio levels. Therefore, dosages (the only available data) alone are not an objective parameter in order to assess the antithrombotic effects of these drugs.

Patients receiving different antiplatelet agents comprised the second group of the study. As aspirin was notably the most popular medication, a partial analysis was conducted selectively only for aspirin patients. However, we consider this rather obligatory, taking into account the limited number of patients in the other antiplatelet subgroups. A distinctive approach in a study with increased number of patients in each subgroup could more accurately delineate the true role of each agent. Regarding cancer staging, we chose to use only the main TNM cancer stages, i.e., stage I, II, III, IV in the study design in order to reach the study end points, at the cost, however, of the reduced prognostic correspondence.

As the higher intake of calcium and vitamin D has been associated with a reduced risk of CRC in epidemiological studies and polyp recurrence in polyp-prevention trials, data regarding oral calcium supplementation in the patients included in the study were provided^[11]. Generally, the administration of oral calcium and folic acid, another possible chemopreventive agent^[12], supplements in both groups of the study was equally low. The elimination of possible bias emanating from the possible chemopreventive action of calcium or other agents on CRC stage that could possibly interfere with the results of the study was the main argument for this approach.

According to our data, tumor related bleeding, either chronic manifested as anemia or acute per rectum blood loss that dictated the endoscopic assessment, was more frequent in the antithrombotic arm of the study ($P = 0.002$). This susceptibility to hemorrhage that patients receiving antiplatelet medication exhibit as an adverse side effect seems beneficial in unmasking an existent CRC at an earlier stage ($P = 0.007$). The partial analysis, only for aspirin patients, yielded respective results ($P = 0.003$) resolving initial fears for bias from the approach to group all antiplatelet agents together in the analysis.

Differences in the incidence of each cancer stage in the two groups were also observed. The incidence of advanced stage IV disease was lower in the antiplatelet group of the study ($P = 0.033$). Generally, in the given patient sample, patients on antiplatelet medication tended to have a lower mean CRC stage. However, this finding can be underlined with statistical power only for stage IV patients. The increased incidence of early stage disease (stage I, II) in the antiplatelet group, although not statistically significant, could possibly suggest the favorable impact of antiplatelet medication on the earlier CRC diagnosis.

However, a few things should be kept in mind before interpreting the results of the present study and seeking for correspondence in clinical practice. The issues raised in this paper could be only half of the story in CRC patients taking antiplatelets. The retrospective nature of the study and the selection bias represent limitations.

The inclusion criteria for the study were the diagnosis of CRC, either through a selective endoscopy and biopsy or through an emergency investigation due to a tumor related complication. Consequently, patients finally included in the study are a selective population submitted to one surgical unit, rendering the given patient sample not accurately representative of all CRC patients. Additionally, we assume that patients with co-morbidities requiring chronic medications, such as antiplatelets, are generally managed by their physicians more attentively than their control counterparts. In this patient group, the threshold for diagnostic evaluation of cancer related symptoms is logically lowered. This at least theoretical inequality represents another possible limitation. However, differences between the two groups in cancer diagnosis through a screening colonoscopy were not encountered. We had inadequate data regarding patients with benign and/or dysplastic polyps submitted to endoscopic polypectomy alone and consequently these patients were not included in the study. Possibly, the incorporation in the final analysis of patients that the malignant transformation was terminated in the dysplastic polyp stage due to polypectomy would provide more objective results.

Initially, the results of the present study appear to be more an observation with limited clinical significance and usefulness. However, clinical decisions regarding CRC patients can be affected beneficially, based on the results of this study. Third age patients with multiple co-morbidities receiving antiplatelet medication are the most common scenario in clinical practice. In these patients, notable hesitation and increased amount of subjectivity characterize the therapeutic decisions from the surgeon's viewpoint. On the other hand, the diagnosis of an existent CRC at an earlier stage is theoretically associated with an increased likelihood of a feasible surgical resection from the technical and oncological viewpoints. Of course, correlations with the prognosis would be inappropriate, taking into account the co-morbidities present in these patients and the actual cancer stage. The results of the present study can, however, give surgeons the impetus in order to more readily provide this patient group with the opportunity of a surgical procedure with curative intent.

In conclusion, antiplatelet medication seems to be a blessing in disguise for CRC patients. Generally, the adverse effect of bleeding that is justifiably attached to this drug category seems to have a favorable impact on the staging characteristics of an existent CRC.

COMMENTS

Background

Aspirin, also called acetylsalicylic acid, has become a very popular medication, especially among the elderly. As a platelet aggregation inhibitor, it is used in a variety of medical conditions. Besides aspirin, newly introduced antiplatelet agents, such as clopidogrel, are also used in order to reduce the risk of thrombosis recurrence in patients with prior myocardial infarction, stroke or peripheral arterial disease.

Research frontiers

The antithrombotic indications of antiplatelet treatment are well established.

However, there is a scarcity of data regarding the possible favorable effects of antiplatelet treatment on colorectal cancer (CRC) staging characteristics.

Innovations and breakthroughs

In the present study, the authors aimed to evaluate whether antiplatelet treatment leads to the diagnosis of an existent CRC at an earlier stage. According to the data, tumor related bleeding, either chronic manifested as anemia or acute per rectum blood loss that dictated the endoscopic assessment, was more frequent in patients receiving antiplatelet medication. This susceptibility to hemorrhage that patients receiving antiplatelet medication exhibit as an adverse side effect appeared beneficial in unmasking an existent CRC at an earlier stage. The incidence of advanced disease was also lower in patients receiving antiplatelet medication.

Applications

Initially, the results of the present study appear to be more an observation with limited clinical significance and usefulness. However, clinical decisions regarding CRC patients can be affected beneficially, based on the results of this study. Third age patients with multiple co-morbidities receiving antiplatelet medication are the most common scenario in clinical practice. In these patients, notable hesitation and increased amount of subjectivity characterize the therapeutic decisions from the surgeon's viewpoint. On the other hand, the diagnosis of an existent CRC at an earlier stage is theoretically associated with an increased likelihood of a feasible surgical resection from the technical and oncological viewpoints. Of course, correlations with the prognosis would be inappropriate, taking into account the co-morbidities present in these patients and the actual cancer stage. The results of the present study can, however, give surgeons the impetus in order to more readily provide this patient group with the opportunity of a surgical procedure with curative intent.

Terminology

Antiplatelet drugs, such as aspirin, decrease platelet aggregation and inhibit thrombus formation, especially in the arterial circulation, and are commonly administered in high risk patients in order to prevent recurrent cardiac ischemia and cardiovascular events generally. On the other hand, cancer of the colon or rectum, i.e., CRC, is a common adult malignancy. The tumor, nodes and metastasis staging system is the most widely used cancer staging system worldwide.

Peer review

Although this paper is a retrospective study, the authors show an interesting result that the incidence of stage IV disease is lower in patients taking antiplatelet agents compared to the control group.

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