Govaresh/ Vol. 23, No.1, Spring 2018; 53-57.

Brief Report

Anti-Platelet Therapy and the Risk of Upper Gastrointestinal Bleeding

Anahita Sadeghi [1], Mohammad Biglari [2], Farhad Fayaz [2], Ali Ali Asgari [1,*]

[1] Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran.
[2] Department of Internal Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background:
We aimed to determine the effects of anti-platelet drugs use on adverse outcomes in patients with non-variceal upper gastrointestinal bleeding (UGIB).

Materials and Methods:
A historical cohort study was performed on patients with non-variceal UGIB admitted to a tertiary care hospital. Clinical outcomes were compared among users of aspirin and patients who did not receive aspirin. Adverse outcome variables consisted of re-bleeding, need for surgery, and death

Results:
Out of 271 patients (77.5% men, mean age 59.5 ± 19.0 years) with non-variceal UGIB, 157 (57.9%) did not receive any anti-platelet drugs, 87 (32.1%) received only aspirin, and 27 (10.0%) received dual anti-platelet therapy. The frequency of adverse outcomes was significantly higher in patients who bled while not receiving anti-platelets (31.2% no anti-platelets, 12.6% single anti-platelet agent, and 14.8% on dual anti-platelets, $p = 0.002$). A significant difference in the duration of admission was not found between the three groups (5.5 ± 4.3 in patients with no anti-platelet drugs, 5.6 ± 4.6 in patients received single anti-platelet agent, and 5.0 ± 4.3 in patients received dual anti-platelets, $p = 0.84$).

Conclusion:
Patients with non-variceal UGIB while taking anti-platelet drugs had a lower rate of adverse outcomes compared with non-users of anti-platelets.

Keywords: Antiplatelet therapy, Gastrointestinal bleeding, Endoscopy

please cite this paper as:

Sadeghi A, Biglari M, Fayaz F, Ali Asgari A. Anti-Platelet Therapy and the Risk of Upper Gastrointestinal Bleeding. *Govaresh* 2018;23:53-57.

Corresponding author:
Ali Ali Asgari, MD
Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran.
Tel: + 98 21 84902101
Fax: + 98 21 88220000
E-mail: alialiasgari@gmail.com

Received: 12 Nov. 2017
Edited: 19 Feb. 2018
Accepted: 20 Feb. 2018

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is a major clinical problem with considerable morbidity and mortality. Many of such patients require hospital admission and invasive treatment (1). Unfortunately, despite emerging advanced therapeutic techniques, the associated mortality rate is still concerning (2-4).

Anti-platelet agents are a common class of medications used in cardiovascular diseases. It is reported that aspirin is used at least once a week by nearly 60% of US population (5). Gastric mucosal injury caused by aspirin can be triggered by accidental, occasional, or chronic use of this drug and it is now considered as a notorious cause for peptic ulcer disease and associated complications (6-8).

It has been reported that continued use of low dose aspirin in patients with UGIB can reduce all-cause mortality rate while providing beneficial anti-platelet effects as well (9,10). Existing evidence regarding the impact of aspirin on the clinical outcomes of patients with UGIB is still controversial. Some studies have reported that aspirin may reduce mortality rate in these patients (11-13), and some other studies have stated that it has no effects (14,15).

We decided to assess the effect of aspirin on the clinical outcomes of hospital inpatients with non-variceal UGIB in a university-affiliated hospital.

MATERIALS AND METHODS

A historical cohort study was performed on patients with non-variceal UGIB admitted to the emergency department of Shariati Hospital, Tehran. We used the definition of non-variceal UGIB as presentation with signs or symptoms of hematemesis, coffee ground material seen in gastric lavage, or melena. Patients with rectal bleeding associated with hemodynamic instability and patients with confirmed source of bleeding in the upper gastrointestinal (GI) tract on endoscopy were included in the study.

The exclusion criteria were detection of esophageal or fundal varices, bleeding episode occurring during hospital admission, warfarin or any other anticoagulant use, occult UGIB, and endoscopic evaluation performed more than 48 hours after admission.

A comprehensive drug history was taken at the time of admission and the patients were categorized based on aspirin use into three groups: those on aspirin use (n = 87), those on dual anti-platelet therapy with aspirin and clopidogrel (n = 27), and those not taking aspirin or any anti-platelet drugs or non-steroidal anti-inflammatory drugs (NSAIDs) (n = 157). Other obtained data included demographic data, medical history, vital signs, and initial blood tests in emergency ward, and final endoscopic diagnosis.

We documented clinical outcomes including length of hospital admission, re-bleeding events, surgical interventions if any, and inpatient mortality as well as the need for blood transfusion. Re-bleeding was defined as repeated episodes of hematemesis, melena, or coffee ground emesis as well as a hemoglobin drop > 2 g/dL during admission. Any surgical intervention needed to stabilize the patient or stop the bleeding was considered as the need for surgery.

The Rockall risk score was also calculated for each patient. The score tries to identify the patients at risk of poorer outcome following an UGIB event by implementing clinical criteria (i.e. age, co-morbidity, shock), and endoscopic findings (diagnosis, and signs of acute bleeding) (16). The complete Rockall score of more than 2 was considered as high. The composite adverse outcome variables consisted of any documented evidence of at least one of these events: re-bleeding, need for surgery, and death.

Data analyses were done using SPSS software version 21.0 (SPPS Inc., Chicago, Illinois, USA). Categorical analyses were performed using Chi 2 test or analysis of variance where appropriate. P value of less than 0.05 was considered as statistically significant.

RESULT

A total 271 patients (210 men and 61 women; mean age = 59.5 ± 19.0 years) with non-variceal GI bleeding were recruited in our study. Table 1 demonstrates the demographic and clinical characteristics of the patients. The Patients with UGIB and without any prior anti-platelet use were markedly younger and had fewer underlying diseases than those received anti-platelet drugs ($p < 0.01$).

The most common initial presentations in order of frequency were melena (33.2%), hematemesis and melena (22.8%), coffee ground gastric lavage (20.4%), hematemesis only (18.3%), and hematochezia (5.3%). Initial measures of hematocrit, platelet count, or PT were not significantly different between the three groups.

180 patients (66.2%) needed blood transfusion. Hematocrit level was higher than 30% in 110 patients (40.6%), of whom 32.7% (36 patients) received blood transfusion. Endoscopic therapeutic intervention was required for 84 patients (31.0%). Table 2 summarizes major clinical outcomes of the patients.

Final endoscopic diagnoses were as follows: 24 (8.8%) with esophageal source (esophageal erosion/ ulcer, mass, or mallory-weiss lesion), 124 (45.7%) with gastric source (gastric ulcer, erosion, or mass), and 98 (36.2%) with duodenal lesion (ulcer or mass). In 16 patients (6.0%) more than one source was identified and source of bleeding could not be found

Table 1: Demographic and clinical features of the patients regarding the use of anti-platelet drugs

Variables	Aspirin alone (n = 87)	Dual therapy (n = 27)	No anti-platelet (n = 157)	Total (n = 271)
Age, years (Mean ± SD)	66.6 ± 14.1	66.8 ± 12.1	54.3 ± 20.6*	59.5 ± 19.0
Male, n (٪)	67 (77.0%)	23 (85.2%)	120 (76.4%)	210 (77.5%)
Initial lab results (Mean ± SD)				
Hemoglobin (g/dL)	9.8 ± 3.1	9.8 ± 2.8	9.2 ± 2.2	9.4 ± 3.0
PT (Sec)	13.1 ± 2.4	12.9 ± 1.8	13.3 ± 2.3	13.2 ± 2.3
Systolic BP (mmHg)	124.8 ± 24.1	120.1 ± 11.0	116.7 ± 24.5	119.6 ± 25.0
Duration of admission (Mean ± SD)	5.6 ± 4.6	5.0 ± 4.3	5.5 ± 4.3	5.5 ± 4.4

*: $P < 0.05$.
BP: Blood Pressure; PT: Prothrombin Time; SD: Standard Deviation.

Table 2: Outcomes of the patients and comparison between the patients taking aspirin and the patients without anti-platelet therapy

Variables	Taking aspirin (n = 114)	No anti-platelet (n = 157)	Total (n = 271)
Transfusion need, n (%)	71 (62.3%)	109 (69.4%)	91 (66.4%)
Mortality, n (٪)	3 (2.6%)	8 (5.1%)	11 (4.4%)
Surgery, n (٪)	2 (1.7%)	5 (3.2%)	7 (2.6%)
Re-bleeding, n (٪)	12 (10.5%)	42 (26.7%)*	54 (19.9%)
Composite adverse outcome+, n (٪)	16 (14.0%)	48 (30.6%)*	64 (23.6%)

*: $P = 0.001$
+: Composite adverse outcome is defined as presence of mortality, need for surgery, or re-bleeding.

Table 3: Rockall scores comparing the patients with and without aspirin use

Variables	Taking aspirin (n = 114)	No anti-platelet (n = 157)	Total (n = 271)
High complete Rockall score, n (%)+	89 (78.1%)	89 (56.7%)*	178 (65.7%)
High clinical Rockall score, n (٪)+	43 (37.7%)	40 (25.5%)**	85 (31.4%)

*: $P < 0.001$; **: $P = 0.04$
+: Complete Rockall score > 2 and clinical Rockall score > 2 considered high.

in 9 (3.3%) patients. A malignant-appearing mass was diagnosed in 37 patients (13.7%).

Duration of hospital admission was not significantly different between the patients taking aspirin and those without anti-platelet therapy (5.6 ± 4.3 vs. 5.4 ± 4.5; $p = 0.8$). Re-bleeding occurred in 54 patients (19.9%) and seven patients (2.6%) underwent surgical therapeutic intervention. Mortality rate was 4.4% (n = 12). The composite adverse outcome was present in 64 patients (23.6%).

The patients on aspirin alone were more likely to receive a higher complete Rockall score compared with those without anti-platelet therapy (78.6% vs. 56.6%; $p = 0.01$). The prevalence of high clinical Rockall score was also significantly higher among patients taking aspirin than patients with no anti-platelet treatment. Rockall scores are presented in table 3.

Re-bleeding was more common in patients without anti-platelet therapy than patients taking aspirin (26.7% vs. 10.5%; $p = 0.001$). The need for surgical intervention and mortality rate were also less likely in aspirin users compared with patients without aspirin use, but the difference was not significant. The composite adverse outcome was more frequently occurred in patients without any anti-platelet treatment than in patients taking aspirin or on dual anti-platelet therapy (30.8% vs. 13.4%; $p = 0.001$).

DISCUSSION

Non-variceal GIB is a major complication related with the use of anti-platelet and anticoagulant drugs (17,18). On the other hand, these drugs may influence the management and final outcome of patients with UGIB (10,19). Our main finding was that patients who took aspirin had a lower morbidity and mortality compared with those without anti-platelet agents. Some studies have reported the same beneficial effect

for aspirin use in UGIB (11,20). Conversely, others have shown no major association between aspirin use and mortality (15) or suggested worse outcomes (10,21,22).

We compared the patients with UGIB regarding previous consumption of aspirin and interestingly found that although higher Rockall score was seen in patients taking aspirin than patients who received no anti-platelet drugs, they had better prognosis according to composite adverse outcomes. This apparent discrepancy might be attributable to the essence of Rockall scoring system assigning higher scores to patients taking aspirin (assuming cardiovascular diseases), though they might have better outcome.

The rate of re-bleeding was 19.96%, which is similar to previous reports (11,14,20). Previous data show that aspirin use may be associated with increased risk of re-bleeding (12,23). Nonetheless, our study revealed that re-bleeding was significantly less prevalent in patients on aspirin contributing to fewer composite outcomes. This may be accountable by the so-called aspirin rebound phenomenon (24,25) saying that discontinuing anti-platelet drugs may have a prothrombotic effect.

In our study, length of hospital admission was somehow higher than others (10-12), which might be due to referral and educational nature of our centre. Length of hospital admission was not related to aspirin use, which is consistent with some previous studies (12). However, some other studies showed shorter (11) or longer (10) hospitalization. Varied study designs or non-homogenous patient selection included in these studies might be the reason.

This survey is of importance because we aimed to assess the effect of anti-platelet consumption with a variety of adverse outcomes. Furthermore, it included patients in a tertiary care center with standardized techniques and equipments. However, there were some limitations. First of all, the patients taking anticoagulants were excluded from the study and the sample size of the patients on dual therapy was limited, thus the results are not generalizable to patients taking anti-platelets only. Secondly, we have studied in-hospital mortality and morbidity and the patients were not followed up for a longer period, therefore a longer ante grade cohort study might be needed to assess long-time effects of anti-platelets in patients with UGIB.

In conclusion, we showed that aspirin intake might have favorable outcomes in non-variceal GIB. More studies are required to confirm this effect in more heterogeneous populations.

ACKNOWLEDGEMENT

The authors thank the Research and Development Center of Shariati Hospital for helping on the statistical aspects of this manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

REFERENCES

1. Wang YR, Richter JE, Dempsey DT. Trends and outcomes of hospitalizations for peptic ulcer disease in the United States, 1993 to 2006. *Ann Surg* 2010;251:51-8.
2. Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: Patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011;60:1327-35.
3. Sung JJ, Tsoi KK, Ma TK, Yung MY, Lau JY, Chiu PW. Causes of mortality in patients with peptic ulcer bleeding: a prospective cohort study of 10,428 cases. *Am J Gastroenterol* 2010;105:84-9.
4. Cooper GS, Yuan Z, Rosenthal GE, Chak A, Rimm AA. Lack of gender and racial differences in surgery and mortality in hospitalized Medicare beneficiaries with bleeding peptic ulcer. *J Gen Intern Med* 1997;12:485-90.
5. Talley NJ, Evans JM, Fleming KC, Harmsen WS, Zinsmeister AR, Melton LJ III. Nonsteroidal antiinflammatory drugs and dyspepsia in the elderly. *Dig Dis Sci* 1995;40:1345-50.
6. Liberopoulos EN, Elisaf MS, Tselepis AD, Archimandritis A, Kiskinis D, Cokkinos D, et al. Upper gastrointestinal haemorrhage complicating anti-platelet treatment with aspirin and/or clopidogrel: where we are now? *Platelets* 2006;17:1-6.
7. Yasuda H, Yamada M, Sawada S, Endo Y, Inoue K, Asano F, et al. Upper gastrointestinal bleeding in patients receiving dual anti-platelet therapy after coronary stenting. *Inter Med* 2009;48:1725-30.
8. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of

proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of anti-platelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation* 2010;122:2619-33.

9. Hsu PI. New look at anti-platelet agent-related peptic ulcer: An update of prevention and treatment. *J Gastroenterol Hepatol* 2012;27:654-61.
10. Taha AS, Angerson WJ, Knill-Jones RP, Blatchford O. Upper gastrointestinal mucosal abnormalities and blood loss complicating low-dose aspirin and antithrombotic therapy. *Aliment Pharmacol Ther* 2006;23:489-95.
11. Abu Daya H, Eloubeidi M, Tamim H, Halawi H, Malli AH, Rockey DC, et al. Opposing effects of aspirin and anticoagulants on morbidity and mortality in patients with upper gastrointestinal bleeding. *J Dig Dis* 2014;15:283-92.
12. Sung JJ, Lau JY, Ching JY, Wu JC, Lee YT, Chiu PW, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2010;152:1-9.
13. Marmo R, Koch M, Cipolletta L, Capurso L, Grossi E, Cestari R, et al. Predicting mortality in non-variceal upper gastrointestinal bleeders: validation of the Italian PNED score and prospective comparison with the Rockall score. *Am J Gastroenterol* 2010;105:1284-91.
14. van Leerdam ME, Vreeburg EM, Rauws EA, Geraedts AA, Tijssen JG, Reitsma JB, et al. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. *Am J Gastroenterol* 2003;98:1494-9.
15. Mose H, Larsen M, Riis A, Johnsen SP, Thomsen RW, Sørensen HT. Thirty-day mortality after peptic ulcer bleeding in hospitalized patients receiving low-dose aspirin at time of admission. *Am J Geriatr Pharmacother* 2006;4:244-50.
16. Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal hemorrhage. *Gut* 1996;38:316-21.
17. García Rodríguez LA, Lin KJ, Hernández-Díaz S, Johansson S. Risk of upper gastrointestinal bleeding with low-dose acetylsalicylic acid alone and in combination with clopidogrel and other medications. *Circulation* 2011;123:1108-15.
18. Barada K, Abdul-Baki H, El Hajj II, Hashash JG, Green PH. Gastrointestinal bleeding in the setting of anticoagulation and antiplatelet therapy. *J Clin Gastroenterol* 2009;43:5-12.
19. Wolf AT, Wasan SK, Saltzman JR. Impact of anticoagulation on rebleeding following endoscopic therapy for nonvariceal upper gastrointestinal hemorrhage. *Am J Gastroenterol* 2007;102:290-6.
20. Lanas A, Aabakken L, Fonseca J, Mungan ZA, Papatheodoridis GV, Piessevaux H, et al. Clinical predictors of poor outcomes among patients with nonvariceal upper gastrointestinal bleeding in Europe. *Aliment Pharmacol Ther* 2011;33:1225-33.
21. Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. *BMJ* 2006;333:726.
22. Lin KJ, De Caterina R, García Rodríguez LA. Low-Dose Aspirin and Upper Gastrointestinal Bleeding in Primary Versus Secondary Cardiovascular Prevention: A Population-Based, Nested Case–Control Study. *Circ Cardiovasc Qual Outcomes* 2014;7:70-7.
23. Li L, Geraghty OC, Mehta Z, Rothwell PM, Oxford Vascular Study. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. *Lancet* 2017;390:490-9.
24. Alcock RF, Reddel CJ, Pennings GJ, Hillis GS, Curnowc JL, Brieger DB. The rebound phenomenon after aspirin cessation: The biochemical evidence. *Int J Cardiol* 2014;174:376-8.
25. Lordkipanidzé M, Diodati JG, Pharand C. Possibility of a rebound phenomenon following antiplatelet therapy withdrawal: A look at the clinical and pharmacological evidence. *Pharmacol Ther* 2009;123:178-86.