Original Research Article

Prevalence and pattern of NSAID consumption among patients with upper gastrointestinal bleeding

ABSTRACT

Introduction: Gastrointestinal bleeding is one of the most common causes of patient admissions at emergency wards. Despite considering NSAIDs, aspirin and Helicobacter pylori as the leading causes, mortality from GI bleeding is still high. So pattern of NSAID consumption and related conditions may help in preventative behavior.

Methods: This case-control study was conducted on 300 patients. Patients were divided into two groups: with and without gastrointestinal bleeding. Patient's information was extracted using their hospital records and the data eventually was statistically analyzed.

Results: The results of this study showed that the frequency of NSAIDs use was significantly higher in patients with gastrointestinal bleeding (P = 0.016) with the most NSAID use as Aspirin. The prevalence of smoking, using drugs and alcohol consumption was significantly higher in the study group (P <0.05).

Conclusion:A history of consuming NSAIDs increases the risk of GI bleeding. The frequency of cigarette, drug, and alcohol consumption in the case study group was significantly higher than that of the control group.

Keywords: Gastrointestinal bleeding, Nonsteroidal anti-inflammatory drugs, aspirin

Introduction:

Gastrointestinal (GI) bleeding is the most common reason for acute hospitalization of patients in gastroenterology wards(1). Different studies have evaluated the implemented cost of GI bleeding on both patients

and the health care system, in addition to its impact on mortality and morbidity rates.These studies have concluded that GI bleeding, in fact, incurs higher patient and system costs and raises mortality and morbidity rates(2, 3).Several factors have been propounded as etiologic factors behind GI bleeding, among which H.pylori,Non-Steroid Anti-Inflammatory Drugs (NSAIDs), and aspirin have been deemed as the most significant, especially in upper GI bleeding(4). Different epidemiologic studies have suggested that a combination of several different NSAIDs,or a high dose of any one of these drugs, can increase the risk of GI bleeding up to seven and nine fold respectively(5). These results emphasizenot only the importance of NSAIDs but alsotheir sensible usage. Recently, due to the increased prevalence of arthritic diseases and osteoarthritis, the use of NSAIDs has grown. The prescription of multiple NSAIDs to patients by different physicians in various fields has led tothe increased simultaneousconsumption of several NSAIDs. This raises the risk of GI bleeding and other NSAID side effects, especially among the older population.

In consideration of the rising usage of NSAIDs, it is imperative to study the correlation between the use of NSAIDs and upper GI bleeding. Although this relationship is now mentioned in textbooks, there has not yet been any related study conducted in Mashhad, Iranto explorethe

high prevalence of NSAID consumption, this despite numerous warnings aboutthe side effects following the unbridled use of these drugs. Furthermore, since accurate statistics about NSAID side effects are critical for future prophylaxis recommendations, it appears beneficial to conducta study on the correlation between upper GI bleeding and NSAID consumption.

Method and Materials:

The present case control study was conducted in several steps. These steps were performed simultaneously and by only one researcher in order to reduceany possible risk of error. The steps were designed as a checklist for utilizationin the present study, by which samples were chosen, data extracted and collected, and statistical calculations made.

Checklist Design:

The checklist was designed as two forms. The first form was intended for patients hospitalized at the emergency ward of Qaem Hospital due to upper GI bleeding and who had undergone diagnostic and therapeutic measures.This checklist included identification code, gender, age, weight, educational level, occupation, marital status, and residence. Also listed was any history of digestive diseases, GI bleeding, non-digestive diseases,smoking, alcohol consumption, drug abuse,and medications. In addition, the following information was provided:endoscopy results,

primary hemoglobin, primary platelet, primary PT, INR, and the possible need for a blood transfusion.

The second form was designed for patients hospitalized at Khatam-al_Anbia Hospital of Ophthalmology with a chief complaint and reason for hospitalization that was unrelated to GI bleeding (control group). This checklist included the following: identification code, gender, age, weight, educational level, occupation, marital status, and residence.Also listed was any history ofdigestive diseases, GI bleeding, non-digestive diseases, smoking, alcohol consumption, drug abuse, and medications.

Selection of Cases and Control Samples:

The method of sampling in the currentstudy was simple nonrandomized. Two groups were studied. The first group (case group) consisted of patients hospitalized for gastrointestinal bleeding at the emergency ward of Qaem Hospital and who had undergone diagnostic and therapeutic measures. The second group (control group) was made up of patientshospitalized at Khatam-al_AnbiaHospital of Ophthalmology due to a chief complaint and reason for hospitalization unrelated to gastrointestinal bleeding.

Data Extraction and Collection:

In this step of the present study, required data were collected and registered onto the appropriate checklist. The case study group data were collected from the patients' hospital files. The control group data was obtained by conducting direct interviews and also by accessing the patients' previous files. To accomplish this, at Khatam-al Anbia Hospital, the researcher first explained the study and its purpose to the patients and obtained their consent before reviewing files or interviewing.

Statistical Calculations:

First, the data were input into SPSS ver.16 software. The mean and Interquartile rangewere utilized to describe the quantitative data indexes, such as mode.Frequency and frequency percentage served asthe indexes for explainingqualitative data.In order to compare qualitative variables in the case study and control groups, the Chi-squared test or exact fisher test were utilized. If the data had a normal distribution, the independent t-test compared the quantitative data from the two groups; otherwise, its nonparametric equivalent (Man-Whiteny) performed this comparison.The confidence interval and the level of significance were deemed as 95% and 0.05% respectively.

Results:

The present work studied a total number of 300 patients aged above 35. Patients were dividedinto two groups: 1)those suffering from upper GI

bleeding (case study) and 2) those without GI bleeding (control group). The mean age of the patients was 45.81±21.28 years (in the range of 40 to 87 years).

The patient demographicsofthe two groups are compared in Table 1-4 and 2-4. Statistical tests showed no significant difference between the two groups in terms of age, gender, marital status, distribution of weight, and education level (P>0.05). In regard to residence, the resultsindicated a significant difference between that of the case study and the control group(p=0.002).

Table 1-4: Comparisonof Mean and Interquartile Range

§P-value	Control Group (without GI bleeding) Median (IQR)(150n=)	Case Study Group (with GI bleeding) (IQR) Median (150n=)	Variable Group
0.116	(65-45) 54	(65-47) 59	Age

§: Mann-Whitney statistical test

Table 2-4: Comparison of Qualitative Variable Frequency

*P-value	Control Group Frequency & Frequency Percentage	Case Study Group Frequency& Frequency Percentage	Variable Group	
0.726	84 (56%)	88 (58.6%)	male	Gender

	66 (44%)	62 (41.3%)	female	
0.796	40 (26.7%)	45 (28.7%)	single	Marital Status
	110 (73.3%)	105 (71.3%)	married	
0.615	31 (20.7%)	25 (16.6%)	< 50	Weight (kg)
	74 (49.3%)	81 (54%)	50 - 70	
	45 (30%)	44 (29.4%)	>70	
0.107	12 (8%)	12 (8%)	illiterate	Educational Level
	20 (13.3%)	36 (24%)	only reading & writing	
	36 (24%)	32 (21.3%)	up to elementary school	
	51 (34%)	53 (35.3%)	high school diploma	
	25 (16.7%)	13 (8.7%)	associate degree	
	6 (4%)	4 (2.7%)	Bachelor degree&higher	
0.002	124 (82.7%)	94 (62.7%)	city	Residence
	26 (17.3%)	56 (37.3%)	village	

*: Chi-Square statistical test

Table 3-4 compares the two groups' frequency of cigarette and alcohol consumption and drug abuse.As seen, the frequency was significantly higher in the case study group($p<0.05$).In addition, the most common

substance consumed was cigarettes, followed in prevalence by drugs and alcohol respectively.

Table3-4: Comparison of the Consumption of Cigarettes, Drugs, and Alcohol

*P-value	Control Group Frequency & Frequency Percentage	Case Study Group Frequency& Frequency Percentage	Variable Group	
0.001	31 (20.7%)	58 (38.7%)	yes	History of Cigarette Use
	119 (79.3%)	92 (61.3%)	no	
0.004	8 (5.3%)	24 (16%)	yes	History of Drug Abuse
	142 (94.7%)	126(84%)	no	
0.026	4 (2.7%)	14(9.4%)	yes	History of Alcohol Consumption
	146 (97.3%)	136 (90.6%)	no	

*: Fisher Exact statistical test

The frequency of a history of digestive and non-digestive diseases is presented in Table 4-4.As observed, the comparison does not show any significant difference between the case study and the control group.On the other hand,there was a significant difference in the frequency of non-digestive disease history between the two groups (p=0.027).

Table4-4: Comparison of the Frequency of Diseases History 141

P-value*	Control Group Frequency Percentage	Case Group Frequency Percentage	Variable Group	
0.078	38 (25.3%)	50 (33.3%)	yes	History of Digestive Disease
	112 (74.7%)	100 (66.7%)	no	
0.0272	73 (48.7%)	93 (62%)	yes	History of Non-digestive Disease
	77 (51.3%)	57 (38%)	no	

142

143 *: Chi-Square statistical test

144 Table 4-5 provides the frequency of NSAID consumption inthe two
145 groups. As indicated, NSAID consumption in patients with GI bleeding
146 was significantly higher compared to those not suffering from this
147 condition (p=0.016). Furthermore, the comparison among the types of
148 NSAID consumed by patients of the two groups showed a significant
149 difference in regard to type($p<0.001$). The most commonlyused NSAID
150 in the case study group was aspirin, eitheras an ongoing consumption or
151 at least for a past period of time.In fact, except for sixpatients, all
152 subjects in the control group using NSAIDswere taking aspirin. After
153 aspirin, the most common NSAID in the case study group was
154 ibuprofen.However, in the control group, there was greater consumption
155 of ibuprofen followed by aspirin and diclofenac respectively. In both

study groups, other NSAIDs, such as indomethacin and naproxen,were less commonly used.

Table 4-5 : Comparison of the frequency of NSAID consumption and its subtypes

	35 (23.4%)	55 (36%)	yes	NSAID Consumption
0.022**	115 (76.6%)	95 (64%)	no	
	13 (8.7%)	49 (32.66%)	Aspirin	Type of NSAID
	14 (3.9%)	5 (34.3%)	Ibuprofen	
	7 (7.4%)	0 (0%)	Diclofenac	
*0.001<	0 (0%)	1 (7.0%)	Indomethacin	
	1 (7.0%)	0 (0%)	Naproxen	
	0 (0%)	0 (0%)	Other	

*: Chi-Square statistical test
**: Fisher Exact statistical test

The frequency of othermedications taken by patients is presented in Table 6-4. A significant difference inthetype of drugs taken is evident between the two groups (p=0.035).In the case study group, the most common were corticosteroids (15.3%),Warfarin (14%), and Plavix (13.3%). However,in the control group, the most prevalent drugs were SSRIs (10.6%), Plavix (4), and corticosteroids (4%). Generally, the amount of medications taken by the case study patients was significantly

higher. In both groups,the consumption of Heparin was less than any other of the drugs.

Table 6-4: Comparison of the Frequency of Other Drug Consumption

P-Value*	Control Group Frequency & Frequency Percentage	Case Study Group Frequency& Frequency Percentage	Other Drugs
0.038	5(%3.3)	21 (14%)	Warfarin
	6(4%)	20 (%13.3)	Plavix
	6(4%)	23 (%15.3)	Corticosteroids
	5(%3.3)	15 (10%)	Other NSAIDs
	16(%10.6)	14 (%9.3)	SSRIs
	2(%1.3)	8 (%5.3)	Heparin

*:Chi-Square statistical test

Table 7-4 provides patient endoscopy results.As seen,out of 150 patients with GI bleeding, 97 had undergone anendoscopy while the other 53 patients had not because ofvarious reasons, such as patient unwillingness or medical conditions. The most common pathologic finding followingendoscopy was ulcers (38.1%), while a mass was the

least commonly observed pathology (4.2%).In 20.6 % of the patients, the endoscopy resultswere normal.

Table 7-4: Frequency of Endoscopic Findings in Patients with Upper GI Bleeding

Frequency Percentage	Frequency	Variable	
20.6%	20	Normal	Endoscopy Results
38.1%	37	Observed Ulceration	
23.7%	23	Observed Inflammation	
6.2%	6	Observed Varicose	
4.2%	4	Observed Mass	
7.2%	7	Other	

The results of the coagulative and hemoglobin tests of patients with upper GI bleeding are also given in Table 8-4. As observed, the mean amount of hemoglobin was 10.23 gr/dl and that of platelets was 235000 per microliter, with hemoglobin results being less than normal. In addition, the PT, PTT, and INR indexes of the patients showed that the amount of PT was 16.3 and INR 1.41, indexes that are slightly higher than normal. The mean PTT was 30.42%, which is in the normal range.

The logistic regression test was employed to assess the extent of the studied variables' prediction effect on GI bleeding.As seen, in a

comparison between the case study and the control group,cigaretteuse, alcohol consumption, and, finally,a history of NSAID consumption can lead to an increased risk of upper GI bleeding incidence with an OR of 1.81,4.241, and 1.838 respectively.

From these variables, drug abuse, gender, and age did not have any effect onraising or lowering the risk of upper GI bleeding incidence. Table 8-4 liststhe results for each studied variable.

Table 8-4: Evaluating the Predictive Effect of Variables under Study on the Establishment of GI Bleeding

CI 95% for OR (lower-upper)	Odds Ratio(OR)	P-value**	Variable
0.942-1.004	0.965	0.175	Age
0.634-1.664	1.029	0.92	Gender*
1.071-3.151	1.838	0.024	Cigarette Use
0.941-5.459	2.72	0.06	Drug Abuse
1.415-13.29	4.421	0.02	Alcohol Use
1.076-3.067	1.812	0.021	History of NSAID

*risk of males compared to females

Logistic regression test**

Discussion

In the presentresearch, a total of 300 patients aged above 35 were studied in two groups. One group consisted of subjects suffering from GI bleeding and the other group of subjects without this condition.Statistical tests revealed that there was no significant difference between the two groups in regard to gender frequency,age,maritalstatus, weight group frequency, and educational level.However,the statistical tests did reveal that there was a significant difference between the two study groups where patient residence was concerned; patients in the control group more frequently lived in urban areas, a finding that had barelybeen investigatedpreviously.For instance, the Button et al. study conducted in2010 showed that ahigher number of patients with upper GI bleeding lived in urban areas(6). Likewise, in the 2012 study by Whiskey et al., the prevalence of varicose and non-varicose upper GI bleeding was reported to be greateramong the urban population(7).Yet, thesetwo above mentioned studies did not further explore the possible reasons behind their findings. In any case, it seems that the stronger presence of risk factors for upper GI bleeding in urban areas has led to a greater number of patients in these areas. Furthermore, in the case of the present study,the location of Qaem Hospital in the urban center of Mashhad may explain the higher incidence of GI bleeding in the area. As a matter of fact, the urban population served by Qaem Hospital is larger

thanthe number of its patients from rural areas, which can explain the greater prevalence of upper GI bleeding reported in the present research.

Based on the current study's results, it can be said that the case study and control group were rather similar in regard to demographic variables that can affect upper GI disease;there was an appropriate selection of the groupsand the background risk factors were alike.

The present research's other findings suggest that the prevalence of cigarettesmoking, alcohol consumption, and drug abuse was significantly higher in the case study groupwhen compared to the control group. Furthermore, by studying the predictive effects of upper GI bleeding, it was observed that variables, such as alcohol, cigarettes, and drug abuse,raise the risk of upper GI bleeding in patients. These findings have also been reported in other similar studies. For example, the Crooks et al. 2013 study found thatcigarette use (whether active or passive) and alcohol consumption increased the risk of upper GI bleeding (non-variceal GI bleeding).In the case control study, 16,355 patients with upper GI bleeding were compared to subjectssimilar in age, gender, and occupation. As for alcohol consumption,the study also reported that the risk of bleeding incidence grew following a rise in consumption. Lastly, alcohol and cigarette consumption were deemed as significant risk factors for upper GI bleeding and the study noted the

importance of focusing on these(8). The results of the research are completely in accordance with the present work. Another US study in 2016 investigated the risk of GI bleeding in patients with a history of cigarette or alcohol use. 48,000 men between the ages of 40 to 75 were tracked for a period of 26 years. The results reported 305 cases of GI bleeding. In the analysis of the variables of alcohol and cigarette consumption by the research subjects, drinking more than 30 gr of alcohol per day was shown to increase the risk of GI bleeding as opposed to the abstaining control group. Furthermore, consuming alcohol more than 5 times per week was deemed to be an independent risk factor increasing the incidence of GI bleeding. The study also suggested that cigarette use is not related to GI bleeding(9).Despite no correlation found between smoking and GI bleeding by the study, the results were more or less in accordance with those ofthe current research in thatalcohol consumption was reported as a GI bleeding risk factor.

The relation between alcohol and upper GI bleeding has been explored by other studies as well, many of which were case controls investigating the correlation between alcohol consumption and different causes of upper GI bleeding, such as pepticulcer (10).However, research looking specifically into the link between alcohol consumption and upper GI bleeding is generally in theminority(9, 11). However, those studies

observed a strong correlation that is in accordance with the currentwork. From a biological perspective, the relation between alcohol consumption and GI bleeding is valid as it is now understood that alcohol can lead to desquamation of the gastricepithelium, edematouschange in the lamina properia, tissue necrosis in deep layers, and also bleedingerosions. Alcohol related mucosal damagecan be caused by a rise in the production of oxygen-free radical species,a fall in the level of prostaglandins, and also the release of mucosal leukotrienes(12, 13).

As for cigarette smoking and upper GI bleeding, different results have been reported by various studies. This factor requires larger population size for evaluation. Similar to the current work, someresearchers have propounded cigarettes as a risk factor for GI bleeding, while some others have not(9, 14, 15).

In regard to a history of GI disease, some research has reported no significant difference between the case study and the control group. However, there has been a significant difference observed when comparing the history of non-digestive disease frequency. In the UK, Hearnshaw et al. studied 6,750 patients suffering from GI bleeding. It was found that 50% of the patients studied had at least one of the followingdiseases: ischemic heart disease, heart failure, respiratory disease,brain stroke,dementia, cancer,andcirrhosis, all of which are associated with a higher risk of mortality. Similar to the present work, the

study reported a high number of patients with upper GI bleeding who also suffered from several other non-digestivediseases. Itmust be noted, however, that, unlike the present research, the study did not include a control group, thus making comparisons impossible(16).Another study by Rockall et al. assessed upper GI bleeding risk factors and found that many non-digestive diseases are related to an increased risk of upper GI bleeding. These diseases includeischemic heart disease, heart failure, asthma, chronic pulmonary obstructive diseases, kidney failure, renal failure, cancer, dementia, hypertension, and pneumonia. Similar to the Hearnshaw et al. research, the study observed a correlation between the prevalence of these diseases and a higher mortality risk among patients(17).The relation between upper GI bleeding and some specific diseases has been previously reported. As an example, in 2000, Weil et al. found a higher rate of upper GI bleeding in diabetic patients as compared to a non-diabeticpopulation(10). Similarly, Kalman and Petrosa studied patients with renal diseases and indicated a higher rate of gastric disease and especially upper GI bleedingwhen compared to a normal population. Other studies share the same findings(18, 19). In agreement with the present research, the studies presented above all recognizethe link betweennon-digestive diseases in the incidence of upper GI bleeding.Ingeneral, it appears that patientssuffering from

different diseases also have an increased risk of both the incidence of upper GI bleeding and a higher mortality rate.

In the present study's comparison of NSAID consumption between the case study and control group, there was a significant difference in the type of NSAIDused. Except for sixpatients, all of the case study patients had used NSAIDs,of which aspirin was the most commonly consumed followed by ibuprofen.Patients in the control group, however, had comparatively higher ibuprofen consumption,with aspirin being the second most common drug consumed. After aspirin, the control group used Diclofenac at a higher rate than that of the case study patients.Bothgroups had a lower consumption of other types ofNSAIDs, such as indomethacin and naproxen.In conclusion,the present study generally associatesaspirin consumption with greater GI bleeding. This finding has also been noted in several previous studies. For example, the 2012 review article by Castellsague et al. concluded that Ibuprofen, the most commonly used drug in the control group, is the safest NSAID from the aspect of upper GI bleeding(20). Also, in their 2012 study, De Abajo et al. investigated the relation of NSAIDs and other drug consumption with upper GI bleeding. It was revealed that aspirin poses a higher risk of upper GI disease than the consumption of other drugs(21).The results of the two studies described above are in accordance with the present work's findings in that the case study and

control group most commonly consumed aspirin and ibuprofenrespectively.

Another result of the present study addresses the frequency of other drug consumption by the patients of the two groups. In both the case study and the control group, a large spectrum of drugs were taken by patients,out of which the current work attempted to discern which are closer related to upper GI bleeding. The findings show a significant difference in the amount of drugs consumed by the two groups. Among the cases study subjects, the most common were corticosteroids (15.3%), Warfarin (14%), and Clopidogrel (13.3%). However, the most prevalent medications for control group subjects were SSRIs (10.6%), clopidogrel (4%), and corticosteroids (4%). In general, the drug consumption in the case study group was significantly higher. In both groups, Heparin was the least used. Previous studies have also investigated the correlation between the use of various drugs and upper GI bleeding. For instance,the 2014 review of 159 articles by Narum et al. studied the link between corticosteroids and upper GI bleeding.It was finally concluded that corticosteroids use is associated with an increased risk of upper GI bleeding and gastric ulcers(22). As mentioned in the present study,using these drugs in the case study group was more than in the control group. Regarding Warfarin and Clopidogrel and their relation to upper GI bleeding, previously conducted studies concur with

366 thecurrentpaper's findings. In 2013, De Abajo et al. investigated the use
367 of these drugs in patients with upper GI bleedingand concluded that their
368 consumption can heighten the risk of upper GI bleeding in comparison to
369 healthy individuals(21). The subjects in the present paper's case study
370 group also took more multiple NSAIDs than did the control group.
371 Previous studies have stressed that the consumption of multiple NSAIDs
372 increase the risk of upper GI bleeding. After exploring the risk factor of
373 upper GI bleeding in their 2010 research, Scarpiganto and Hunt
374 concluded that taking multiple NSAIDs or anticoagulant drugs, such as
375 Warfarin and corticosteroids, all can increase the risk of gastric
376 bleedings,a finding with which the present paper is in accordance(23).
377 The current paper's other results deal with patient endoscopies. 97
378 patients with GI bleeding underwent endoscopy while the other 53
379 patients did not for reasons such as medical issues orunwillingness to
380 consent to the procedure. The most common pathologic finding was
381 ulcers, which were observed in 38.1% of patients undergoing
382 endoscopy, while the least common pathology was a mass as observed
383 in 4.2% of these patients. In 20.6% of the patients, the endoscopy
384 results were normal. In the 2011Hearnshaw et al. study of 6,750 patients
385 with upper GI bleeding, the most commonly observed pathology was
386 ulcers,with inflammation as the second most prevalent(16),findings
387 similar to those ofthe current research.

The other result of the present study dealt with the hemoglobin, platelet, and coagulation profiles of patients suffering from upper GI bleeding,as provided in the results section. The mean amount of blood hemoglobin of these patients was 10.32 gr/dl, indicating a low and thus anemia. It must be noted that blood tests were only conducted onsubjects with upper GI bleeding and so comparison against the control group was regrettably not possible. However, in consideration of the subjects' GI bleeding, low readings in reported blood hemoglobin, in comparison with normal results, can be expected. In Hearnshaw et al.'s study, the mean amount of hemoglobin in patients was also low at 11gr/dl, again below the normal cut-off(16). In addition, Gonzalez-Gonzalez et al. reported a low mean amount of 9.2 gr/d, again less than normal(24).

Conclusion:

The results of the present study indicate that greater consumption of NSAIDs in patients with upper GI bleeding is significantly higher in comparison with patients not suffering from this condition. Moreover,a history of consuming NSAIDs increases a patient's risk of acquiring GI bleeding. Likewise, the frequency of cigarette, drug, and alcohol consumption in the case study group was significantly higher than that of the control group,thus signifying that variables, such as alcohol and cigarettes, increase the risk of GI bleeding in patients.

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