Original Research Article

A case-control study on the risk of UGIB in patients taking NSAIDs in Mashhad, Iran

Comment [81]: No acronyms in the title

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.

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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.

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Results: The results of this study showed no significant difference between the two groups in terms of age, gender, marital status, distribution of weight, and education level (P>0.05). The frequency of NSAIDs use was significantly higher in patients with gastrointestinal bleeding (P = 0.016) with the most NSAID use as Aspirin(32.66%). The prevalence of smoking, using drugs and alcohol consumption was significantly higher in the study group (P <0.05).

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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:

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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

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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 a study on Northeast of Iran Zeinali et al showed that about 20% of all prescriptions included at least one NSAID drugs in comparison with 12.1% in USA (6).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 relatedstudy conducted in Mashhad, Iranto explorethe high prevalence of NSAID consumption, this

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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 (6).

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. All the patients were asked for NSAID use (continuously or based on need).

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 according to clinical manifestation and/or diagnostic endoscopic examinationat the emergency ward of Qaem Hospital. The second group (control group) was made up of patients hospitalized at Khatam-al_Anbia Hospital of Ophthalmology due to a chief complaint and reason for hospitalization unrelated to gastrointestinal bleeding.

Data Extraction and Collection:

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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. Frequency and frequency percentage served as the indexes for explaining qualitative 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 (Mann-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

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Comment [824]: The mean takes standard deviation, while the median takes inter-quartile range. Why you mix things wrongfully? Refer to a statistician to edit your work.

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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 demographics of the two groups are compared in Table 1 and 2. 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 results indicated a significant difference between that of the case study and the control group(p=0.002).

Table 1: Comparison of Mean and Interquartile Range of demographic variables

Variable Group		Case Study Group (with GI bleeding) (IQR) Median (150n=)	Control Group (without GI bleeding) Median (IQR)(150n=)	P-value
§Age		(65-47) 59	(65-45) 54	0.116
Gender	male	88 (58.6%)	84 (56%)	0.726
	female	62 (41.3%)	66 (44%)	
Weight (kg)	< 50	25 (16.6%)	31 (20.7%)	0.615
	50 -70	81 (54%)	74 (49.3%)	
	>70	44 (29.4%)	45 (30%)	

123   *§:*   Mann-Whitney statistical test

124

125   **Table 2:** Comparison of Qualitative demographic Variable Frequency

Variable Group		Case Study Group Frequency& Frequency Percentage	Control Group Frequency & Frequency Percentage	*P-value
Marital Status	single	45 (28.7%)	40 (26.7%)	0.796
	married	105 (71.3%)	110 (73.3%)	
Educational Level	illiterate	12 (8%)	12 (8%)	0.107
	only reading & writing	36 (24%)	20 (13.3%)	
	up to elementary school	32 (21.3%)	36 (24%)	
	high school diploma	53 (35.3%)	51 (34%)	
	associate degree	13 (8.7%)	25 (16.7%)	
	Bachelor degree&higher	4 (2.7%)	6 (4%)	

Residence	city	94 (62.7%)	124 (82.7%)	0.002
	village	56 (37.3%)	26 (17.3%)	

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127 *: Chi-Square statistical test

128 Figure-1compares the two groups' frequency of cigarette and alcohol

129 consumption and drug abuse.

130 **Figure 1:**Comparison of the Consumption of Cigarettes, Drugs, and

131 Alcohol
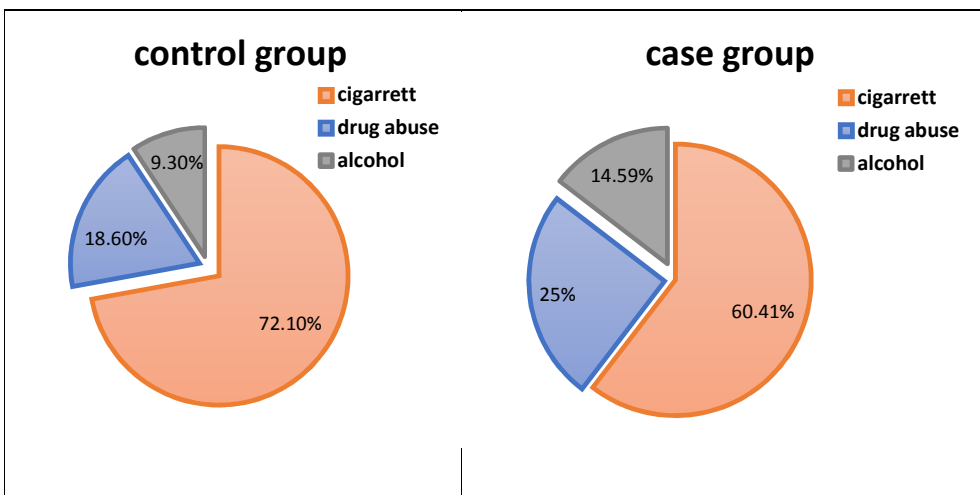
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133 Table 3 provides the frequency of NSAID consumption inthe two groups.

134 As indicated, NSAID consumption in patients with GI bleeding was

135 significantly higher compared to those not suffering from this condition

136 (p=0.022).Furthermore, the comparison among the types of NSAID

137 consumed by patients of the two groups showed a significant difference

in regard to type(p<0.001). The most commonlyused NSAID in the case study group was aspirin 80 mg per day, either as an ongoing consumption or at least for a past period of time.In fact, except for sixpatients, all subjects in the control group using NSAIDs were taking aspirin. After aspirin, the most common NSAID in the case study group was ibuprofen. However, in the control group, there was greater consumption of ibuprofen followed by aspirin and diclofenac respectively. In both study groups, other NSAIDs, such as indomethacin and naproxen,were less commonly used.

Table 3: Comparison of the frequency of NSAID consumption and its subtypes

		control	case	p-value
NSAID Consumption	yes	35 (23.4%)	55 (36%)	0.022**
	no	115 (76.6%)	95 (64%)	
Type of NSAID	Aspirin	13 (8.7%)	49 (32.66%)	*<0.001
	Ibuprofen	14 (9.3%)	5 (3.34%)	
	Diclofenac	7 (4.7%)	0 (0%)	
	Indomethacin	0 (0%)	1 (0.7%)	

	Naproxen	1 (0.7%)	0 (0%)
	others	0(0%)	0(0)%)

150

151 *: Chi-Square statistical test

152 **: Fisher Exact statistical test

153

154 The frequency of other medications taken by patients is presented in

155 figure 2. A significant difference inthetype of drugs taken is evident

156 between the two groups (p=0.035). In the case study group, the most

157 common were corticosteroids (15.3%), Warfarin (14%), and Plavix

158 (13.3%). However, in the control group, the most prevalent drugs were

159 SSRIs[1] (10.6%), Plavix (4%), and corticosteroids (4%). In both groups,

160 the consumption of Heparin was less than any other of the drugs.

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Comment [838]: ? We do not use footnotes anymore in formal manuscript writing. Identify the acronym fully first time and them use abbreviation.
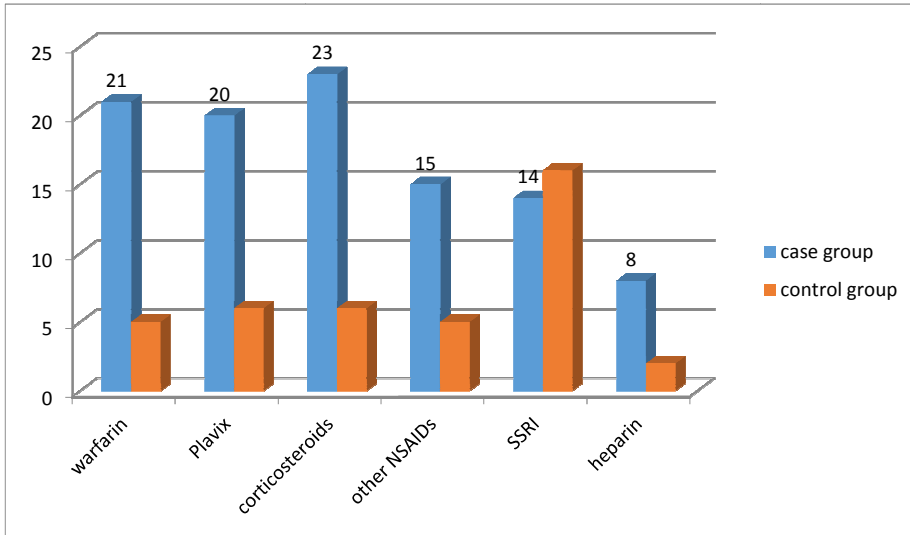
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[1] Specific Serotonin Receptor Inhibitors

Comment [840]: Drugs

Figure 2: Comparison of the Frequency of Other Drug Consumption


Figure 3 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 following endoscopy was ulcers (38.1%), while a mass was the least commonly observed pathology (4.2%). In 20.6 % of the patients, the endoscopy results were normal.

Figure 3: Frequency of Endoscopic Findings in Patients with Upper GI Bleeding
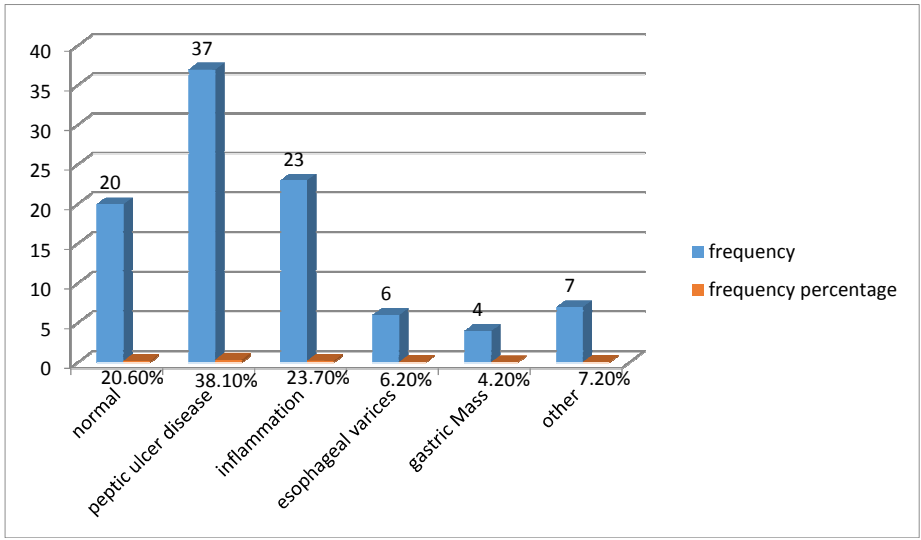
The logistic regression test was employed to assess the extent of the studied variables' prediction effect on GI bleeding. As seen, in a comparison between the case study and the control group, cigarette use, alcohol consumption, and, finally, a history of NSAID consumption can lead to an increased risk 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 4 lists the results for each studied variable.

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

Variable	CI 95% for OR (lower-upper)	Odds Ratio(OR)	P-value**

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Age	0.942-1.004	0.965	0.175
Gender*	0.634-1.664	1.029	0.92
Cigarette	1.071-3.151	1.838	0.024
Drug abuse	0.941-5.459	2.72	0.06
Alcohol Use	1.415-13.29	4.241	0.02
NSAID Use	1.076-3.067	1.812	0.021

*risk of males compared to females 191

Logistic regression test** 192

Discussion 193

194 In the present study, statistical tests revealed that there was no

195 significant difference between the two groups in regard to gender

196 frequency, age, marital status, weight group frequency, and educational

197 level. The study revealed that patients in the case group more frequently

198 lived in urban areas, a finding that had barelybeen

199 investigatedpreviously.For instance, the Button et al. study conducted

200 in2010 showed that ahigher number of patients with upper GI bleeding

201 lived in urban areas(7). Likewise, in the 2012 study by Whiskey et al.,

202 the prevalence of variceal and non-variceal upper GI bleeding was

203 reported to be greateramong the urban population(8).Yet, these two

204 above mentioned studies did not further explore the possible reasons

205 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.

The present research suggest that the prevalence of cigarette smoking, alcohol consumption, and drug abuse was significantly higher in the case study group when compared to the control group. 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.The study also reported that the risk of bleeding incidence grew following a rise in alcohol consumption (9). Another US study in 2016 revealed that drinking more than 30 gr of alcohol per day or 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 (10). Alcohol related mucosal damage can 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(11, 12).

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, some researchers have propounded cigarettes as a risk factor for GI bleeding, while some others have not(10, 13, 14).

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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 NSAID used. Except for six patients, 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. Aspirin was used at a dose of 80 mg per day in both groups and unfortunately the dose of NSAIDs were not available which was the limitation of the present study. After aspirin, the control group used Diclofenac at a higher rate than that of the case study patients. Both groups had a lower consumption of other types of NSAIDs, such as indomethacin and naproxen. In conclusion, the present study generally associates aspirin 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(15). 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(16).These results are in accordance with the present work's findings.

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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 by Narum et al. finally concluded that corticosteroids use is associated with an increased risk of upper GI bleeding and gastric ulcers(17). 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 thecurrentpaper's findings. In 2013, De Abajo et al. concluded that Clopidogrel consumption can heighten the risk of upper GI bleeding in comparison to healthy individuals(16). The subjects in the present

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paper's case study group also took more multiple NSAIDs than did the control group. Previous studies have stressed that the consumption of multiple NSAIDs increase the risk of upper GI bleeding. After exploring the risk factor of upper GI bleeding in their 2010 research, Scarpiganto and Hunt concluded that taking multiple NSAIDs or anticoagulant drugs, such as Warfarin and corticosteroids, all can increase the risk of gastric bleedings,a finding with which the present paper is in accordance(18).

The current paper's other results deal with patient endoscopies. 97 patients with GI bleeding underwent endoscopy while the other 53 patients did not for reasons such as medical issues orunwillingness to consent to the procedure. The most common pathologic finding was ulcers. In the 2011Hearnshaw et al. study of 6,750 patients with upper GI bleeding, the most commonly observed pathology was ulcers (19),findings similar to those of the current research.

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. Aspirin and Ibuprofen were the most two common drugs used. Moreover,a history of consuming NSAIDs increases a patient's risk of acquiring GI bleeding. Concurrent consumption of corticosteroids, Warfarin and clopidogrel increased the risk of GI bleeding in case group. Likewise, the frequency

294 of cigarette, drug, and alcohol consumption in the case study group was

295 significantly higher than that of the control group,thus signifying that

296 variables, such as alcohol and cigarettes, increase the risk of GI

297 bleeding in patients.

298 We suggest to consider the factors that increase the risk of upper GI

299 bleeding in patients with NSAID use and prescribe prophylaxis to high

300 risk patients.

301 Ethical Approval Disclaimer:

302 This research was approved at ethical committee of Mashhad University

303 of Medical Sciences with ethical code:922817

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305 Consent Disclaimer:

306 As per international standard or university standard, patient's consent

307 has been collected and preserved by the authors.

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