

Prevalence and pattern of NSAID consumption among patients with uppergastrointestinal bleeding_ a case-control study

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 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 ($P < 0.05$).

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

29 have evaluated the implemented cost of GI bleeding on both patients
30 and the health care system, in addition to its impact on mortality and
31 morbidity rates. These studies have concluded that GI bleeding, in fact,
32 incurs higher patient and system costs and raises mortality and morbidity
33 rates(2, 3). Several factors have been propounded as etiologic factors
34 behind GI bleeding, among which H.pylori, Non-Steroid Anti-Inflammatory
35 Drugs (NSAIDs), and aspirin have been deemed as the most significant,
36 especially in upper GI bleeding(4). Different epidemiologic studies have
37 suggested that a combination of several different NSAIDs, or a high dose
38 of any one of these drugs, can increase the risk of GI bleeding up to
39 seven and nine fold respectively(5). These results emphasize not only
40 the importance of NSAIDs but also their sensible usage. Recently, due to
41 the increased prevalence of arthritic diseases and osteoarthritis, the use
42 of NSAIDs has grown. The prescription of multiple NSAIDs to patients by
43 different physicians in various fields has led to the increased
44 simultaneous consumption of several NSAIDs. This raises the risk of GI
45 bleeding and other NSAID side effects, especially among the older
46 population.

47 In a study on Northeast of Iran Zeinali et al showed that about 20%
48 of all prescriptions included at least one NSAID drugs in comparison with
49 12.1% in USA (6). In consideration of the rising usage of NSAIDs, it is

50 imperative to study the correlation between the use of NSAIDs and
51 upper GI bleeding. Although this relationship is now mentioned in
52 textbooks, there has not yet been any related study conducted in
53 Mashhad, Iran to explore the high prevalence of NSAID consumption, this
54 despite numerous warnings about the side effects following the unbridled
55 use of these drugs. Furthermore, since accurate statistics about NSAID
56 side effects are critical for future prophylaxis recommendations, it
57 appears beneficial to conduct a study on the correlation between upper
58 GI bleeding and NSAID consumption (6).

59 **Method and Materials:**

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

65 Checklist Design:

66 The checklist was designed as two forms. The first form was intended for
67 patients hospitalized at the emergency ward of Qaem Hospital due to
68 upper GI bleeding and who had undergone diagnostic and therapeutic
69 measures. This checklist included identification code, gender, age,
70 weight, educational level, occupation, marital status, and residence. Also

71 listed was any history of digestive diseases, GI bleeding, non-digestive
72 diseases, smoking, alcohol consumption, drug abuse, and medications. In
73 addition, the following information was provided: endoscopy results,
74 primary hemoglobin, primary platelet, primary PT, INR, and the possible
75 need for a blood transfusion.

76 The second form was designed for patients hospitalized at Khatam-
77 al-Anbia Hospital of Ophthalmology with a chief complaint and reason for
78 hospitalization that was unrelated to GI bleeding (control group). This
79 checklist included the following: identification code, gender, age, weight,
80 educational level, occupation, marital status, and residence. Also listed
81 was any history of digestive diseases, GI bleeding, non-digestive
82 diseases, smoking, alcohol consumption, drug abuse. All the patients
83 were asked for NSAID use (continuously or based on need).

84 Selection of Cases and Control Samples:

85 The method of sampling in the current study was simple nonrandomized.
86 Two groups were studied. The first group (case group) consisted of
87 patients hospitalized for gastrointestinal bleeding according to clinical
88 manifestation and/or diagnostic endoscopic examination at the
89 emergency ward of Qaem Hospital. The second group (control group)
90 was made up of patients hospitalized at Khatam-al-Anbia Hospital of

91 Ophthalmology due to a chief complaint and reason for hospitalization
92 unrelated to gastrointestinal bleeding.

93 Data Extraction and Collection:

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

101 Statistical Calculations:

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

112 **Results:**

113 The present work studied a total number of 300 patients aged above 35.
114 Patients were divided into two groups: 1) those suffering from upper GI
115 bleeding (case study) and 2) those without GI bleeding (control group).
116 The mean age of the patients was 45.81 ± 21.28 years (in the range of 40
117 to 87 years).

118 The patient demographics of the two groups are compared in **Table 1 and**
119 **2.** Statistical tests showed no significant difference between the two
120 groups in terms of age, gender, marital status, distribution of weight, and
121 education level ($P > 0.05$). In regard to residence, the results indicated a
122 significant difference between that of the case study and the control
123 group ($p = 0.002$).

124 **Table 1:** Comparison of Mean and Interquartile Range

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%)	

125 §: Mann-Whitney statistical test

126

127 **Table 2:** Comparison of Qualitative 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	13 (8.7%)	25 (16.7%)	

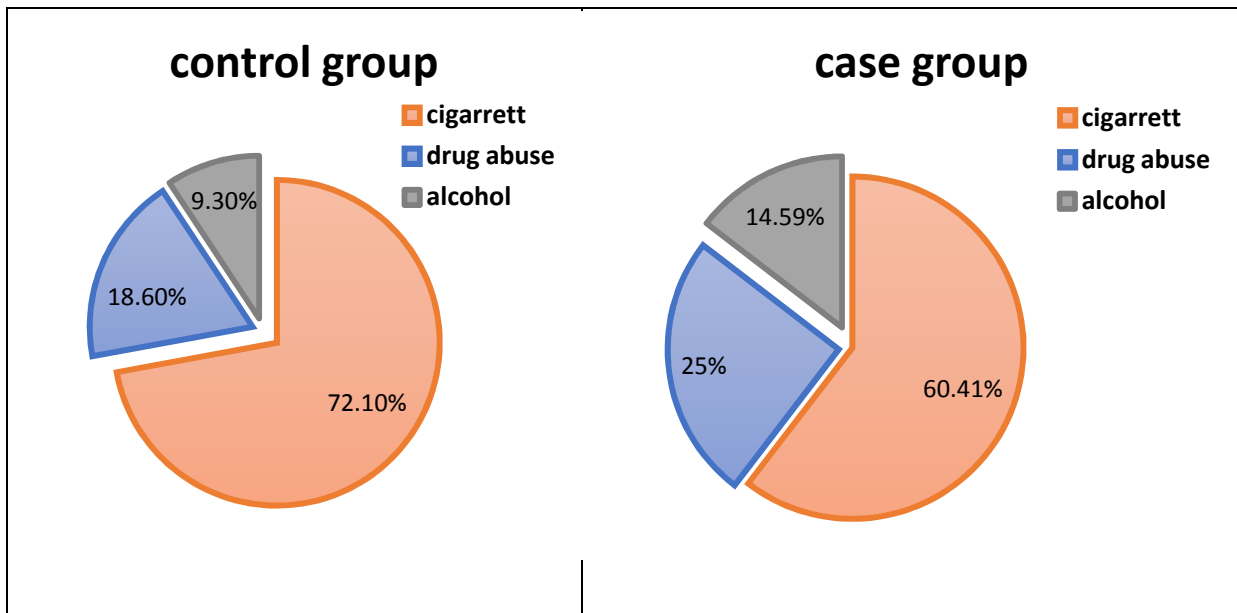
	degree			
	Bachelor degree&higher	4 (2.7%)	6 (4%)	
Residence	city	94 (62.7%)	124 (82.7%)	0.002
	village	56 (37.3%)	26 (17.3%)	

128

129 *: Chi-Square statistical test

130 Figure-1 compares the two groups' frequency of cigarette and alcohol
 131 consumption and drug abuse.

132 **Figure 1:** Comparison of the Consumption of Cigarettes, Drugs, and
 133 Alcohol



134

135 **Table 3** provides the frequency of NSAID consumption in the two groups.
 136 As indicated, NSAID consumption in patients with GI bleeding was
 137 significantly higher compared to those not suffering from this condition
 138 ($p=0.016$). Furthermore, the comparison among the types of NSAID
 139 consumed by patients of the two groups showed a significant difference
 140 in regard to type ($p<0.001$). The most commonly used NSAID in the case
 141 study group was aspirin, either as an ongoing consumption or at least for
 142 a past period of time. In fact, except for six patients, all subjects in the
 143 control group using NSAIDs were taking aspirin. After aspirin, the most
 144 common NSAID in the case study group was ibuprofen. However, in the
 145 control group, there was greater consumption of ibuprofen followed by
 146 aspirin and diclofenac respectively. In both study groups, other NSAIDs,
 147 such as indomethacin and naproxen, were less commonly used.

148 **Table 3:** Comparison of the frequency of NSAID consumption and its
 149 subtypes
 150

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%)	

	Ibuprofen	14 (3.9%)	5 (34.3%)* <0.001
	Diclofenac	7 (7.4%)	0 (0%)
	Indomethacin	0 (0%)	1 (7.0%)
	Naproxen	1 (7.0%)	0 (0%)
	yes		

151

152 *: Chi-Square statistical test

153 **: Fisher Exact statistical test

154

155 The frequency of other medications taken by patients is presented in
 156 Table 4. A significant difference in the type of drugs taken is evident
 157 between the two groups ($p=0.035$). In the case study group, the most
 158 common were corticosteroids (15.3%), Warfarin (14%), and Plavix
 159 (13.3%). However, in the control group, the most prevalent drugs were
 160 SSRIs (10.6%), Plavix (4), and corticosteroids (4%). In both groups, the
 161 consumption of Heparin was less than any other of the drugs.

162 **Table 4:** Comparison of the Frequency of Other Drug Consumption

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164

Other Drugs	Case Study Group Frequency & Frequency Percentage	Control Group Frequency & Frequency Percentage	P-Value*
Warfarin	21 (14%)	5 (3.3%)	

Plavix	20 (%13.3)	6(4%)	0.038
Corticosteroids	23 (%15.3)	6(4%)	
Other NSAIDs	15 (10%)	5(%3.3)	
SSRIs	14 (%9.3)	16(%10.6)	
Heparin	8 (%5.3)	2(%1.3)	

165

166 *:Chi-Square statistical test

167 **Table 5** provides patient endoscopy results.As seen,out of 150 patients
 168 with GI bleeding, 97 had undergone anendoscopy while the other 53
 169 patients had not because ofvarious reasons, such as patient
 170 unwillingness or medical conditions. The most common pathologic
 171 finding followingendoscopy was ulcers (38.1%), while a mass was the
 172 least commonly observed pathology (4.2%).In 20.6 % of the patients, the
 173 endoscopy resultswere normal.

174 **Table5**:Frequency of Endoscopic Findings in Patients with Upper GI
 175 Bleeding

176

Variable		Frequency	Frequency Percentage
	Normal	20	20.6%
	Observed Ulceration	37	38.1%

Endoscopy Results	Observed Inflammation	23	23.7%
	Observed Varicose	6	6.2%
	Observed Mass	4	4.2%
	Other	7	7.2%

177

178 The results of the coagulation and hemoglobin tests of patients with
 179 upper GI bleeding are also given in **Table 6**.

180 The logistic regression test was employed to assess the extent of the
 181 studied variables' prediction effect on GI bleeding. As seen, in a
 182 comparison between the case study and the control group, cigarette use,
 183 alcohol consumption, and, finally, a history of NSAID consumption can
 184 lead to an increased risk of upper GI bleeding incidence with an OR of
 185 1.81, 4.241, and 1.838 respectively.

186 From these variables, drug abuse, gender, and age did not have any
 187 effect on raising or lowering the risk of upper GI bleeding incidence.
 188 Table 7 lists the results for each studied variable.

189
190
191

Table 6: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**
Age	0.942-1.004	0.965	0.175
Gender*	0.634-1.664	1.029	0.92
Cigarette Use	1.071-3.151	1.838	0.024
Drug Abuse	0.941-5.459	2.72	0.06
Alcohol Use	1.415-13.29	4.421	0.02
	1.076-3.067	1.812	0.021

*risk of males compared to females 192

Logistic regression test** 193

Discussion 194

195 In the present study, statistical tests revealed that there was no
196 significant difference between the two groups in regard to gender
197 frequency,age,maritalstatus, weight group frequency, and educational
198 level.The study revealedthat patients in the case group more frequently
199 lived in urban areas, a finding that had barelybeen
200 investigatedpreviously.For instance, the Button et al. study conducted
201 in2010 showed that ahiger number of patients with upper GI bleeding
202 lived in urban areas(7). Likewise, in the 2012 study by Whiskey et al.,
203 the prevalence ofvariceal and non-variceal upper GI bleeding was

204 reported to be greater among the urban population(8). Yet, these two
205 above mentioned studies did not further explore the possible reasons
206 behind their findings. In any case, it seems that the stronger presence of
207 risk factors for upper GI bleeding in urban areas has led to a greater
208 number of patients in these areas.

209 The present research's other findings suggest that the prevalence of
210 cigarette smoking, alcohol consumption, and drug abuse was
211 significantly higher in the case study group when compared to the control
212 group. These findings have also been reported in other similar studies.
213 For example, the Crooks et al. 2013 study found that cigarette use
214 (whether active or passive) and alcohol consumption increased the risk
215 of upper GI bleeding. The study also reported that the risk of bleeding
216 incidence grew following a rise in alcohol consumption (9). The results of
217 the research are completely in accordance with the present work.
218 Another US study in 2016 revealed that drinking more than 30 gr of
219 alcohol per day or more than 5 times per week was deemed to be an
220 independent risk factor increasing the incidence of GI bleeding. The
221 study also suggested that cigarette use is not related to GI
222 bleeding(10). Alcohol related mucosal damage can be caused by a rise in
223 the production of oxygen-free radical species, a fall in the level of
224 prostaglandins, and also the release of mucosal leukotrienes(11, 12).

225 As for cigarette smoking and upper GI bleeding, different results have
226 been reported by various studies. This factor requires larger population
227 size for evaluation. Similar to the current work, some researchers have
228 propounded cigarettes as a risk factor for GI bleeding, while some others
229 have not(10, 13, 14).

230 In the present study's comparison of NSAID consumption between the
231 case study and control group, there was a significant difference in the
232 type of NSAID used. Except for six patients, all of the case study patients
233 had used NSAIDs, of which aspirin was the most commonly consumed
234 followed by ibuprofen. Patients in the control group, however, had
235 comparatively higher ibuprofen consumption, with aspirin being the
236 second most common drug consumed. Aspirin was used at a dose of 80
237 mg per day in both groups and unfortunately the dose of NSAIDs were
238 not available which was the limitation of the present study. After aspirin,
239 the control group used Diclofenac at a higher rate than that of the case
240 study patients. Both groups had a lower consumption of other types
241 of NSAIDs, such as indomethacin and naproxen. In conclusion, the
242 present study generally associates aspirin consumption with greater GI
243 bleeding. This finding has also been noted in several previous studies.
244 For example, the 2012 review article by Castellsague et al. concluded
245 that Ibuprofen, the most commonly used drug in the control group, is the
246 safest NSAID from the aspect of upper GI bleeding(15). Also, in their

247 2012 study, De Abajo et al. investigated the relation of NSAIDs and
248 other drug consumption with upper GI bleeding. It was revealed that
249 aspirin poses a higher risk of upper GI disease than the consumption of
250 other drugs(16).The results of the two studies described above are in
251 accordance with the present work's findings in that the case study and
252 control group most commonly consumed aspirin and
253 ibuprofenrespectively.

254 Another result of the present study addresses the frequency of other
255 drug consumption by the patients of the two groups. In both the case
256 study and the control group, a large spectrum of drugs were taken by
257 patients,out of which the current work attempted to discern which are
258 closer related to upper GI bleeding. The findings show a significant
259 difference in the amount of drugs consumed by the two groups. Among
260 the cases study subjects, the most common were corticosteroids
261 (15.3%), Warfarin (14%), and Clopidogrel(13.3%). However, the most
262 prevalent medications for control group subjects were SSRIs (10.6%),
263 clopidogrel (4%), and corticosteroids (4%). In general, the drug
264 consumption in the case study group was significantly higher. In both
265 groups, Heparin was the least used. Previous studies have also
266 investigated the correlation between the use of various drugs and upper
267 GI bleeding. For instance,the 2014 reviewby Narum et al. finally
268 concluded that corticosteroids use is associated with an increased risk of

269 upper GI bleeding and gastric ulcers(17). As mentioned in the present
270 study,usingthese drugs in the case study group was more than in the
271 control group. Regarding Warfarin and Clopidogrel and their relation to
272 upper GI bleeding, previously conducted studies concur with
273 thecurrentpaper's findings. In 2013, De Abajo et al.concluded
274 thatClopidogrel consumption can heighten the risk of upper GI bleeding
275 in comparison to healthy individuals(16). The subjects in the present
276 paper's case study group also took more multiple NSAIDs than did the
277 control group. Previous studies have stressed that the consumption of
278 multiple NSAIDs increase the risk of upper GI bleeding. After exploring
279 the risk factor of upper GI bleeding in their 2010 research,Scarpiganto
280 and Hunt concluded that taking multiple NSAIDs or anticoagulant drugs,
281 such as Warfarin and corticosteroids, all can increase the risk of gastric
282 bleedings,a finding with which the present paper is in accordance(18).

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

290 **Conclusion:**

291 The results of the present study indicate that greater consumption of
292 NSAIDs in patients with upper GI bleeding is significantly higher in
293 comparison with patients not suffering from this condition. Aspirin and
294 Ibuprofen were the most two common drugs used. Moreover, a history of
295 consuming NSAIDs increases a patient's risk of acquiring GI bleeding.
296 **Concurrent consumption of corticosteroids, Warfarin and clopidogrel**
297 **increased** the risk of GI bleeding in case group. Likewise, the frequency
298 of cigarette, drug, and alcohol consumption in the case study group was
299 significantly higher than that of the control group, thus signifying that
300 variables, such as alcohol and cigarettes, increase the risk of GI
301 bleeding in patients.

302 **We suggest to consider the factors that increase the risk of upper GI**
303 **bleeding in patients with NSAID use and prescribe prophylaxis to high**
304 **risk patients.**

305 **Ethical Approval Disclaimer:**

306 This research was approved at ethical committee of Mashhad University
307 of Medical Sciences with ethical code:922817

308

309 **Consent Disclaimer:**

310 As per international standard or university standard, patient's consent
311 has been collected and preserved by the authors.

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