Available online at *www.ujpr.org*
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

Volume 1, Issue 1, 2016

RESEARCH ARTICLE

ROLE OF NON STEROIDAL ANTI-INFLAMMATORY DRUGS IN ACUTE UPPER GASTROINTESTINAL BLEEDING

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ABSTRACT

Objectives: Many patients presented to the causality with upper gastrointestinal bleeding, which is a serious condition associated with significant morbidity and mortality especially in elderly patients and those with coexisting medical diseases. The purpose of the study was to assess the general use of NSAIDs and their relation to upper gastrointestinal bleeding.

Methods: Cross sectional study on patients who were referred for endoscopy for upper gastrointestinal bleeding in Sulaimany Teaching Hospital during the period from January to December 2016. All of them had been exposed to full history taking regarding age, gender, smoking, alcohol and medication used in addition to thorough physical examination and upper gastrointestinal endoscopic examination with biopsy when indicated.

Results: This study enrolled 100 patients with upper GIT bleeding and showed that 48% of those with upper GIT bleeding were using NSAIDs, with male to female ratio of approximately 2:1, and 37 patients (77.1%) of those who were taken NSAIDs, did not use PPI concomitantly.

Conclusion: The study also revealed that elderly patients taking NSAIDs were at higher risk of developing upper GIT bleeding.

Keywords: Gastrointestinal bleeding, NSAIDs.

Article Info: Received 9 August 2016; Revised 3 September; Accepted 15 October, Available online 15 November 2016

Cite this article-
Gharib SM. Role of non steroidal anti-inflammatory drugs in acute upper gastrointestinal bleeding. Universal Journal of Pharmaceutical Research 2016; 1(1): 12-16.
DOI: ***http://doi.org/10.22270/ujpr.v1i1.R4***
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INTRODUCTION

Approximately 50 non-steroidal anti-inflammatory drugs (NSAIDs) are in use throughout the world, the oldest and best known is aspirin. NSAIDs are popular because of their versatile effectiveness as analgesics, antipyretics, and (by definition) as anti-inflammatory agents[1]. Aspirin is also widely used as an anti-thrombotic agent. Unfortunately, aspirin and most other NSAIDs can injure the gastric and duodenal mucosa, with considerable morbidity and mortality[2]. UGI bleeding commonly presents with hematemesis (vomiting of blood or coffee-ground like material) and/or melena (black, tarry stools). A nasogastric tube lavage which yields blood or coffee-ground like material confirms this clinical diagnosis. However, lavage may not be positive if bleeding has ceased or arises beyond a closed pylorus. Gastroduodenal ulcer disease remains a common cause of UGI bleeding. There are four major risk factors for bleeding peptic ulcers[3]. Helicobacter pylori infection, nonsteroidal anti-inflammatory drugs (NSAIDs) stress, gastric acid. Reduction or elimination of these risk factors reduces ulcer recurrence and rebleeding rates[4,5,6,7]. NSAIDs are a common cause of gastrointestinal ulceration[8,9,10,11]. However, all patients with a prior history of bleeding ulcer disease are at increased risk for recurrent ulcer and complications[12,13,14]. NSAIDs also have been implicated as an important factor for non-healing ulcers[15]. Endoscopy is the preferred investigative procedure for upper gastrointestinal bleeding because of its accuracy, low rate of complications and potential for therapeutic intervention[16]. Pathology acute hemorrhagic and erosive gastropathy appears as multiple petechial hemorrhages and small red or black erosions on endoscopy[17,18]. Stress-related lesions (Curling's ulcers) usually appear in the fundus near the gastroesophageal junction and spread distally, but remain confined to the fundus and body[18]. In contrast, gastropathy due to NSAIDs and alcohol involves the entire stomach from the start, although it may be most evident in the antrum[18]. The healthy gastric and duodenal mucosae constitutively use COX- to produce its mucosal protective PGs[18]. Many NSAIDs block COX-1 and COX-2 more or less equally (i.e. are non-selective) and thus impair gastric PG production at low

(<1μM) concentrations, examples include aspirin, indomethacin, ibuprofen, and naproxen. Most drugs that spare COX-1 and selectively inhibit COX-2 have less suppressive effects on gastric PG synthesis, examples include celecoxib and etodolac. As a result, selective inhibitors of COX-2, and also COX–3 inhibitors such as acetaminophen, preserve PG-mediated GI mucosal protection[19,20,21]. However, COX-2 selective inhibitors can lose their specificity for COX-2 at high doses and have the potential to also block COX-1 in the stomach and duodenum and cause damage. American College of Gastroenterology recommendations- A committee appointed by the American College of Gastroenterology has critically reviewed the data regarding the risk factors for NSAID toxicity, and identified the five most important variables that place patients at risk for NSAID related gastrointestinal complications[22].

1. Prior history of an adverse GI event (ulcer, hemorrhage) increases risk four to five fold.
2. Age >60 increases risk five- to six fold.
3. High dosage of a NSAID increases risk 10-fold.
4. Concurrent use of glucocorticoids increases risk four to five fold.
5. Concurrent use of anticoagulants increases risk 10- to 15-fold.

Patients with several risk factors are at highest risk for NSAID-induced GI toxicity (up to 9 percent after six months)[2324], Assessment of these risk factors is recommended for identifying patients who should be considered for prophylaxis if it is felt that an NSAID must be given. Aim of the study includes-

1. To determine the overall causes of upper GIT bleeding.
2. To determine the frequency of NSAIDs induced upper GIT bleeding.
3. To assess local practice in using prophylaxis against NSAIDs induced upper GIT bleeding.

PATIENTS AND METHODS

This study is a cross sectional study. One hundred patients with upper GIT bleeding had been included in this study. They were randomly selected from those who were referred for GIT centre at Sulaimany Teaching Hospital during the period from January to December 2016. All of them had been exposed to full history taking regarding age, gender, smoking, alcohol intake and medication used, in addition to thorough physical examination and upper gastrointestinal endoscopy with biopsy when indicated. We excluded those patients with history of upper GIT bleeding with no endoscopic evidence of bleeding. All of the collected data had been analyzed using Microsoft Excel and Statistical Package for Social Sciences (SPSS) software. The data had been tabulated in form of frequency distribution tables and figures. Student's t-test and Chi-square test had been used for testing the level of significant association or difference between different quantitative and qualitative groups, respectively. A value of less than 0.05 had been selected as the *p* value required determining the significant association or difference.

RESULTS

This study enrolled 100 patients with upper GIT bleeding. The sample included 66 male (66% of the sample) and 34 female patients (34% of the sample). The mean age of the patients was 49.33±14.9 year old (range: 20-80 year old). The mean age of male patients was 50.26±13.7 year old (range: 23-80 year old) and the mean age of the female patients was 47.5±17.1 year old (range 20-70 year old). Twenty nine patients (29% of the sample) were 60 years or older. 49 male patients were younger than 60 years (74.3% of male patients) compared to 22 females patients (64.7% of female patients) were within the same age group.

Table 1: Age and gender distribution of the sample.

Age group	Male		Female		M:F ratio
	No.	%	No.	%	
20-39 year old	17	25.8%	12	35.3	1.4:1
40-59 year old	32	48.5%	10	29.4	3.2:1
≥60	17	25.8%	12	35.3	1.4:1
Total	66	100.0%	34	100.0	1.9:1

It can be seen clearly from Table 2 that total number of patients taken NSAIDs were 48, with 53.63±16.5, and total number of patients who did not taken NSAIDs are 52 with 45.37±12.2 which represent statically significant association between NSAIDs and upper GIT bleeding with calculated t=2.84 and *p* value 0.01, it can also be seen that 82.8% of those aged above 60 year old were taken NSAIDs.

Table 2: Patient's distribution according to their age and history of NSAID use.

Age group	Use NSAIDs		Not use NSAIDs	
	No.	%	No.	%
20-39 year- old	9	31.0%	20	69.0
40-59year old	15	35.7%	27	64.3
≥60 year old	24	82.8%	5	17.2
Total(n=100)	48	48.0%	52	52.2
mean±SD	53.63± 16.5		45.37±12.2	

Calculated t = 2.84, *p* value = 0.01

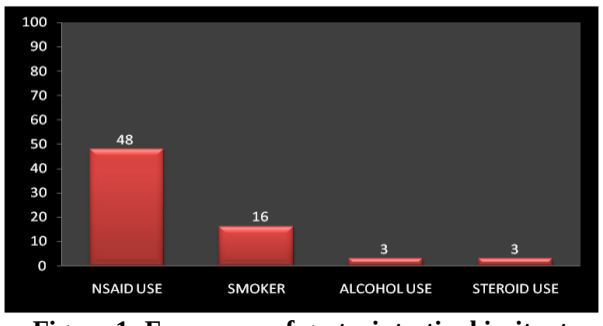

Figure 1: Frequency of gastrointestinal irritant agents.

It can be seen clearly from the Figure 1 that approximately half of those with upper GIT bleeding were taking NSAID, while steroids 3% of the sample, alcohol 3% and 16% of patients were smokers. Figure 2 demonstrate aspirin is the most frequently used drugs

among the NSAID which represent 64.4%, while the selective NSAID usage is only 6.25% from the total usage of NSAID. It had been shown that there was a significant association between the use of NSAIDs in all of their types and the development of upper GIT bleeding (X^2=5.6, p=0.001).

Table 3: Patient's distribution according to their history of NSAIDs and PPI use.

History	Use NSAIDs	
	No.	%
Use PPI	11	22.9%
Did not use PPI	37	77.1%
Total	48	100%

On the other hand no statistically significant association had been observed between use of COX-2 inhibitors and the development of upper GIT bleeding (X^2=1.43, p>0.05).

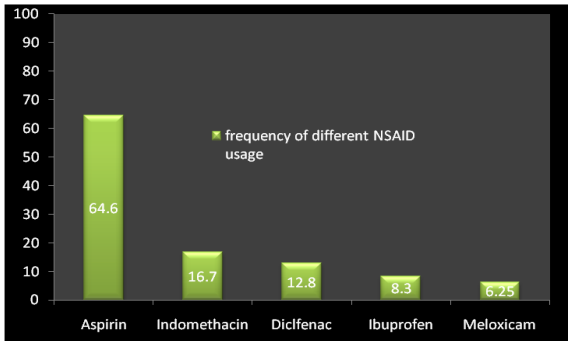

Figure 2: Frequency of different NSAIDs usage.

It can be seen from Table 3 that the majority of patients who use NSAIDs (77.1%) do not use PPI concomitantly, compared to (22.9%) who were using PPI.

Table 4: Patients' distribution according to the endoscopic finding and their history of NSAIDs use.

History	Use NSAIDs		Did not use NSAIDs	
	No.	%	No.	%
Duodenal ulcer	18	34.6	34	65.3
Erosive gastritis	13	61.9	8	38.1
Gastric ulcer	10	76.9	3	23.1
Oesophagitis	3	60	2	40
Oesophageal varices	1	33.3	2	66.7
Gastric malignancy	2	66.7	1	33.3
Mallory Weiss syndrome	0	0	2	100
Gastric arteriovenous malformation	1	100	0	0

DISCUSSION

Acute upper GIT bleeding is a common emergency with important implications for health care costs worldwide. Negative outcomes include rebleeding and death, and many of the deaths are associated with decompensation of coexisting medical condition precipitated by acute bleeding events[25,26]. In a study from one large health maintenance organization, the annual incidence of hospitalization for acute upper GIT bleeding was 102 per 100 000; the incidence was twice as common in males as in females and increased with age[26]. Similar findings were observed in this study which indicated that overall male to female ratio in all age groups was 1.9:1. Furthermore, this phenomenon of higher frequency of upper GIT bleeding was most prominent and evident among those whose age ranged between 40 and 59 year-old with a frequency of upper GIT bleeding among male patients 3 times its frequency among female patients. The M: F ratio showed some decline among those aging 60 years or older, with M: F ratio of about 1.4:1. Examining the data collected from this study showed that in this age group, female patients were more frequently using NSAIDs drugs. In addition, many other studies showed that the impact of NSAIDs on the risk of upper GIT bleeding was greater in women than in men[27,28,29].

Age had been considered as one of five most important risk factors for gastro duodenal toxicity from NSAIDs according to the committee appointed by the American College of Gastroenterology[30]. Similarly, this study showed that elderly patients taking NSAIDs were at higher risk of developing upper GIT bleeding, as 24 out of 29 patients with an age of 60 years or older (82.8%) were taking NSAIDs, In contrast, only 9 out of 29 patients (31%) whose age was 20-39 year-old were taking NSAIDs indicating that the effect of other risk factors for upper GIT bleeding had stronger effect in comparison to the effect of NSAIDs on the frequency of upper GIT bleeding among young patients.

Regarding the history of NSAIDs use including the use of aspirin in all of its recommended doses, many studies with different designs reached the conclusion of considering the use of NSAIDs as a major risk factor in the development of upper GIT bleeding which is the main cause of morbidity and mortality related to NSAIDs use[31,32]. In the United States cohort of rheumatoid arthritis patients alone, it has been estimated that GI toxicity related to NSAIDs use accounts for at least 2600 deaths annually[33]. This study had shown that 48% of those with upper GIT bleeding were using NSAIDs, making the use of NSAIDs the most frequent risk factors for developing upper GI bleeding in the sample enrolled in this study. Lim *et al.*, indicated that over 25% of those with significant upper GIT bleeding were using NSAIDs including COX2 inhibitors[31]. The relatively higher frequency of NSAIDs use among patients enrolled in our study (48% in our study versus 25% in Lim's study) can be attributed to the current trends in our community where drugs are available without proper prescription by an authorized physician; this makes a lot of NSAIDs as an over the shelf medicine with more frequent use as an analgesic. This study indicated that different types of NSAIDs had different frequency of usage in patients with upper GIT bleeding. On reviewing the results of similar studies, the risk of gastrointestinal complications was highest with indomethacin and putting ibuprofen at the bottom of the list[34]. Another potentially important finding that can be derived from this study is that COX2 inhibitors are the least frequent risk factor for upper GI bleeding in our sample (6.25% of the sample).

The first trial is the CLASS study which involved 8059 patients and found that over the initial six months of therapy, COX2 inhibitors were associated with significantly fewer symptomatic ulcers and ulcer complications than ibuprofen or diclofenac[35]. A second trial (the SUCCE- SS-I study) included a total of 13, 274 patients with osteoarthritis from 39 countries and found that there was a reduction in gastrointestinal complications only in patients not taking concomitant aspirin i.e. COX2 inhibitors only[36]. The cornerstone in approaching the problem of NSAIDs induced gastrointestinal toxicity is the primary prevention of such a catastrophic adverse effect[32]. Proton pump inhibitors (PPIs) are useful for the prevention of NSAIDs induced ulcers[37,38,39]. In an illustrative study, the combined incidence of gastric and duodenal ulcers detected endoscopically was reduced in patients who were also treated with 20 mg omeprazole per day (3.6% versus 16.5% with placebo at 6 months)[40]. Unfortunately, our study only 11 out of 48 patients using NSAIDs (22.9%) were taking PPIs for the prevention of NSAIDs induced GIT bleeding. This study revealed that NSAIDs use was more frequently associated with gastric mucosal injury. Twenty three out of 34 patients (67.6%), diagnosed endoscopically as having a gastric mucosal injury in the form of either erosive gastritis (13 patients) or gastric ulcer (10 patients), were using NSAIDs. This higher frequency of gastric mucosal injury in association with NSAIDs use in comparison to less frequent injuries to other parts of GI tract, can be related to the fact that gastric mucosa. This protective mechanism can be inhibited by a very low dose of aspirin or other NSAIDs. Cryer *et al*., found that aspirin doses as low as 10 mg/day can inhibit gastric prostaglandin generation considerably and can damage the stomach[18]. In contrast, some studies showed that aspirin doses as low as 325 mg/day every other day increase the risk of duodenal ulcer[42]. Although the risk of gastric mucosal injury is increased with increasing dose of NSAIDs depending on the finding of several epidemiological and placebo controlled studies[43,44,45], but lower doses of NSAIDs are required to initiate gastric mucosal injury compared to the high doses.

CONCLUSION AND RECOMMENDATIONS

Elderly patients who were taken NSAIDs associated with significant upper GIT bleeding, and their uses were without prophylactic PPI cover in high risk individuals. Below are the recommendations of present study-

1. We have to increase public and physician awareness of NSAIDs side effects, and limit its usage whenever possible
2. To cover NDAIDs usage with prophylactic PPI in high risk groups.

ACKNOWLEDGEMENTS

Author extends his thanks and appreciation to the Ministry of Health KRG, Sulaimani City, Iraq to provide necessary facilities for this work.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTERESTS

None to declare.

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