Original Research Article

A study on clinical profile and risk factors in drug induced UGI bleeding

S. Appandraj[1*], V. Sakthivadivel[2]

[1,2]Associate Professor, Dept. of General Medicine, Karpaga Vinayaga Institute of Medical Sciences and Research, Chinna Kolambakkam, Tamil Nadu, India
[*]Corresponding author email: **dr_appandraj.@yahoo.co.in**

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Abstract

Back ground: It is highly unfortunate that many patients are admitted daily with hematemesis and or malena due to the adverse effects of drugs either prescribed or self-medicated. Incidence of such cases can be greatly reduced if medical practitioners are not only aware of the adverse effects of drugs on gastrointestinal tract but also assess the patients for the risk factors of drug-induced UGI bleeding before prescribing these drugs and also by properly educating the patients.
Aim: To study the clinical profile and risk factors in fifty cases of drug induced UGI bleeding.
Materials and methods: Fifty patients (32 males and 18 females) admitted with drug-induced hematemesis and or malena were studied with respect to age group, number of bouts of hematemesis, approximate quantity of total blood loss, causative drug responsible for UGI bleeding, risk factors of GI bleeding, number of individual risk factors in each patients. The prevalence of individual risk factors in those fifty patients and the prevalence of number of risk factors in those fifty patients were studied. Thorough clinical and laboratory investigations were done.
Results: Hematemesis was the common symptom. Ibuprofen was responsible for the majority of cases (38%) followed by diclofenac (22%). Prevalence of risk factors among the patients are as follows: Age $\geq$ 50 years of age - 66%, 'O' Blood group – 50%, Alcoholism – 42%, Not using Gastro protective agents – 40%, Self-medication / OTC drugs – 36%, Smoking – 30%, Stress and Serious systemic illnesses – 12%, Helicobacter pylori – 12%, Known Peptic ulcer disease – 10% **,** High doses/ Chronic drug intake – 10%, Concomitant use of Steroids – 8% and Concomitant use of anticoagulants – 4%.
Conclusion: NSAIDs were the commonest cause for UGI bleeding. Age $\geq$ 50 years (66%) was the commonest risk factor for UGI bleeding. All those fifty cases had at least one known risk factor and majority (80%) had more than one risk factors of drug-induced UGI bleeding.

Key words

UGI bleeding, NSAID, Hematemesis, Malena, PUD and H.pylori.

Introduction

Peptic Ulcer Disease (PUD) results from the imbalance between the defensive factors that protect the mucosa and offensive factors that disrupt the important gastric mucosal barrier. Many of the primary ulcers seen in teenagers are now thought to be associated with Helicobacter pylori infection while many of the secondary ulcers are due to use of NSAIDs including aspirin. World over, 35 million people consume NSAIDs including aspirin on a daily basis, and about 30% of these users may develop GI toxicity of sufficient degree requiring a physician's intervention. Conservative calculations estimate that approximately 1,07,000 patients are hospitalised annually for NSAID-related gastrointestinal complications, and at least 16,500 NSAID- related deaths occur each year among arthritis patients alone. Surprisingly, the management of this problem has undergone little change in the past 50 years, and is not only frequently under-diagnosed but also under-treated [1]. Indian studies have shown that NSAIDs including aspirin are among the most common drugs responsible for adverse drug reactions seen in clinical practice. In general, at least 10 to 20 percent of patients have dyspepsia while taking an NSAID, although the prevalence may range from 5 to 50 percent. Incidence of new ulcer cases following NSAID intake, ranges from 10% to 40% for gastric ulcers and 5% - 15% for duodenal ulcers. Most patients are, however asymptomatic [2]. Seventy percent of the patients admitted with drug induced UGI bleeding were $\geq$ 50 years of age. According to prospective data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), 13 of every 1,000 patients with rheumatoid arthritis who take NSAIDs for one year have a serious gastrointestinal complication. In India, quacks also practice these drugs commonly and elderly are the most affected [2, 3].

Materials and methods

The study was conducted in the department of general medicine in Karpaga Vinayaga Institute of Medical Sciences and Research from march 2015 to march 2016. Fifty patients satisfying the following inclusion criteria and not having any of the exclusion criteria were taken up for the study.

Inclusion criteria

- All adult patients of both sexes who were giving definite history of intake of drugs and subsequently developed vomiting of frank blood or coffee ground coloured vomit and/or passed dark coloured stools were chosen for this study.
- Inpatients admitted for other illnesses and who subsequently developed UGI bleeding following prescription with drugs like aspirin, other NSAIDs, steroids, anticoagulants and other gastro toxic drugs were also included.
- Standard definitions of hematemesis and malena were used when abstracting data from the clinical records.

Exclusion criteria

- Patients with past history of hematemesis and or malena
- UGI endoscopy finding of other causes of UGI bleeding (e.g. Varices, Mallory weiss syndrome etc.)
- Bleeding and clotting disorders
- Cirrhosis of liver with portal hypertension
- Hematological disorders
- Critically ill patients with life expectancy < 72 hr.

Patient characteristics like age and sex were noted. Detailed history regarding the UGI bleeding like, number of times of hematemesis, approximate quantity of blood vomited each time, associated with malena or presenting with

malena alone and past history of hematemesis and or malena were obtained. Symptoms of GI toxicity of the drugs, symptoms of common diseases that can lead to UGI bleeding and symptoms due to blood loss were recorded in the questionnaire and detailed history regarding the drug and risk factors were asked. Routine general and systemic examination of the patients was carried out with the aim of assessing the general condition of the patient, confirmation of UGI bleeding by Ryle's tube aspiration and/or per rectal examination and assessing severity of blood loss and Ruling out other common causes of gastrointestinal bleeding like cirrhosis of liver with portal hypertension.

Laboratory investigations

Routine urine and blood investigations to find out diabetes, renal failure, hepatic failure and hematological disorders were carried out. Blood grouping and typing was done not only for transfusion of blood but also to find out the role of blood group 'O' in drug- induced UGI bleeding. Serological test for H.pylori (demonstration of anti- H.pylori IgG) was done to find out the association of this bacterium with drug-induced UGI bleeding.

Results and Discussion

In our study, number of patient ≥ 50 years of age was 66%, comprising 2/3 of all the patients (**Table – 1**). In this present study, it was found that the elderly patients ≥ 50 years of age were frequently prescribed NSAIDs and aspirin for their orthopedic and cardiac problems and the relative risk was 2.0 times higher than the others. In Griffin et al study the relative risk for elderly patients with age group of ≥ 65 years was 3.8 times than the others [4]. In an Indian study by Vikas, et al., seventy percent of the patients admitted with drug induced UGI bleeding were ≥ 50 years of age. The lesser average life span of Indian population, early onset of arthralgia, arthritis, low backache, sciatica, spondyloses and coronary artery heart diseases in our population may be the reasons for the higher prevalence of drug induced UGI bleeding at an earlier age compared to the western population [4].

Table – 1: Prevalence of drug-induced UGI bleeding related to age group and sex.

Age group	Male patients	Female patients	Total	%
Age ≤ 19	0	0	0	0%
Age 20 – 34	6	3	9	18%
Age 35 – 49	5	3	8	16%
Age 50 - 64	16	8	24	48%
Age 65 – 79	4	4	8	16%
Age ≥ 80	1	0	1	2%
Number of patients	32	18	50	100%

Sex

Out of the fifty patients studied, thirty two were male patients which gave the male: female ratio of 1.77:1 (**Table – 1**). In a Scandinavian study, it was found that the incidence of drug induced UGI bleeding was twice as high among men as among women [5].

Severity of hematemesis

Percentage of patients with one or two episodes of hematemesis was 72% and 54% of the patients were having minor UGI bleeding (< 100 ml). Only 8% of the patients had severe UGI bleeding (> 1000 ml) in the present study and majority of those patients were found to have four or more risk factors. None of the patients studied, died during the hospital stay. Mortality is high in patients, already known to have peptic ulcer disease, who are taking NSAIDs in high doses

for prolonged period and in patients who are concomitantly taking steroids and anticoagulants [6] as per **Table - 2**.

Table – 2: Frequency of hematemesis.

Number of bouts of Hematemesis	Number of patients
One	18
Two	18
Three	4
Four	5
Five	2

Causative drugs

Ibuprofen was responsible for the majority of cases (38%) followed by diclofenac (22%) as per **Table - 3**. Both drugs had already been proved to be safer than the other nonselective NSAIDs in the previous studies. Aspirin was hardly ever used in the management of chronic arthritic conditions and was mainly prescribed for cardiac patients in low doses (150 mgs). These three drugs were responsible for 76% of all the cases of drug-induced UGI bleeding and tell us the fact that all NSAIDs including aspirin even in safer doses can cause serious GI complications. Aspirin was the only drug found to have been taken regularly for prolonged period, in this study. Although the bleeding risk increases in proportion to NSAID dose, any doses of NSAIDs (including low-dose aspirin taken for cardiovascular prophylaxis) may cause bleeding [7]. It was found in the study that the NSAID nimesulide which was banned few years back was still prescribed in 6% of cases and it was available over the counter in 2% of cases and nimesulide was responsible for UGI bleeding in 8% of the patients studied. Most of the patients (18), who got the drugs over the counter, chose ibuprofen (9) or diclofenac (8). None of the patients in this study took COX-2 selective inhibitor.

High doses / Chronic drug intake

In the present study, only 10% of the patients were taking drugs for longer period $\geq$ 3 months. All of them were taking aspirin for their cardiac illnesses. The risk of bleeding increases with incremental doses of aspirin and most NSAIDs especially with ibuprofen, diclofenac and piroxicam [3]. Risk of deaths due to NSAIDs induced severe GI bleeding, is high in patients taking higher doses of NSAIDs for years [8].

Table – 3: Causative drugs and number of patients.

Causative drugs	Number of patients
Aspirin	8
Diclofenac	11
Ibuprofen	19
Indomethacin	4
Mefenamic acid	3
Nimesulide	4
Piroxicam	1

Self-medication / OTC

A large study involving 421 patients admitted to a hospital in United Kingdom with upper gastrointestinal hemorrhage, who took NSAIDs, revealed that non-prescription drug use was an important cause of bleed in 30% of patients [9, 10]. In the present study, self-medication was observed in 36% of patients. Seven of the eighteen female patients studied (38.89%) took NSAIDs on their own, while eleven of the thirty two male patients (34.38%) were found self-medicated. Ibuprofen (50%) and diclofenac (44.44) were the drugs preferred by seventeen of the eighteen patients who took the drug over the counter.

Drug intake without Gastroprotective agents

Gastroprotective agents are often co-prescribed with NSAIDs, with the aim to reduce the associated GI adverse effects. Co-prescribing rates range from 17 to 34% in the literature [11]. The most commonly used GPAs include proton pump inhibitors (PPIs), H_2 receptor antagonists (H_2RA) and misoprostol. Parenteral PPIs are the most efficacious of all the gastroprotective drugs in patients with NSAIDs-induced UGI bleeding [5]. In our study, 40% of the patients didn't take a gastroprotective drug along with NSAID.

Others took either antacids (34%) or H_2 receptor antagonists (26%).

Known PUD

The use of any NSAID, including low-dose (i.e., ≤ 150 mg/day) aspirin, was associated with an increased risk of GI bleeding in a patient with known peptic ulcer disease and NSAIDs including aspirin should never be taken on an empty stomach [12]. In this study, one male patient and four female patients with peptic ulcer disease, took NSAID and developed UGI bleeding.

Alcoholism and Smoking

Ethanol is known to cause gastric mucosal irritation and nonspecific gastritis. As the quantity of alcohol consumption increased, the relative risk of upper GI bleeding also increased, up to a relative risk of 2.8 in heavy alcohol consumers [13]. In the present study alcoholism was found in 42% of patients with UGI bleeding all of them were males. Also, alcoholism emerged as the third most important independent risk factor for UGI bleeding in this study. Smoking is found to be associated with a threefold elevation in the risk of UGI bleeding in patients taking NSAIDs compared with no smoking. Also the relapse rate of duodenal ulcer is higher in smokers compared with non-smokers. In the current study, 30% of the patients were having the risk factor of smoking and all of them were males. Only one smoker in this study had H.pylori infection and known peptic ulcer disease.

Stress and Serious systemic illnesses

In Manucherhr, et al study, ICU patients with UGI bleeding, 23.95% had respiratory failure, 19.79% had CNS problems and 16.79% had cardiovascular dysfunction, 12.27% had Sepsis [14]. In the present study 12% of patients were having serious systemic illnesses. They had been suffering from coronary artery heart diseases (4 patients) or COPD with respiratory failure (2 patients) and all of them were male patients.

Concomitant use of Steroids and Anticoagulants

Glucocorticoids lead to atrophy of all epithelial tissues including gastro intestinal mucosa and their role in ulcerogenesis is relatively small. Steroids when combined with low doses of aspirin or non-selective NSAIDs or COX-2 selective inhibitors increase the chances of UGI bleeding four folds [15]. In the present study, concomitant intake of steroids contributed as a risk factor in eight percent of cases of NSAIDs induced bleeding.

Aspirin, in low doses (150 mg) was prescribed along with injection Heparin in 4% of patients studied, for CAHD for four days and was able to cause moderate UGI bleeding (100 ml to 1000 ml) in them. This is one of the frequently used combinations in CAHD patients (in ICCU and general ward inpatients) and this study makes us alert about the increased risk of aspirin induced UGI bleeding when taken along with anticoagulant. Anticoagulants do not cause GI bleeding per se, but they can unmask or aggravate hemorrhage from preexisting lesions [6].

'O' Blood group

In Boren et al study, 52.8% of patients with bleeding duodenal ulcers were found to have 'O' blood group [16]. Study by Kuyvenhoven, et al., in 1999 didn't find any potentiation of 'O' blood group on NSAIDs induced ulceration [17]. In the present study half of all those fifty patients studied were found to have 'O' blood group. It had emerged as the second most important independent risk factor.

H.pylori infection

Most evidence now supports the assertion that H.pylori and NSAIDs are synergistic with respect to the development of PUD. Eradication of H.pylori in the setting of chronic NSAID use is associated with a decreased risk of ulcer bleeding [18]. In the current study, the percentage of patients with drug-induced UGI bleeding, affected with H.pylori was only 12%.

Prevalence of number of risk factors

Of the twelve total numbers of risk factors studied, no one was without a risk factor. Eighty percent of the patients had two or more risk factors of drug- induced UGI bleeding. Majority (28 out of 32) of the male patients had two to four risk factors and majority (14 out of 18) of the female patients had one or two risk factors only (**Table – 4, 5**).

Table – 4: Prevalence of risk factors of drug-induced UGI bleeding.

Risk factor	Male (%)	Female (%)	Total (%)
Age ≥ 50 years	21(42%)	12(24%)	33(66%)
High doses/Chronic drug intake	5 (10%)	0	5(10%)
Self-medication / OTC	11 (22%)	7 (14%)	18(36%)
Drug intake without GPA	12 (24%)	8 (16%)	20(40%)
Known PUD	1 (2%)	4 (8%)	5(10%)
Alcoholism	21 (42%)	0	21(42%)
Smoking	15 (30%)	0	15(30%)
Stress & SSI	6 (12%)	0	6(12%)
Steroids	2 (4%)	2 (4%)	4 (8%)
Anticoagulants	2(4%)	0	2 (4%)
'O' Blood group	16 (32%)	9 (18%)	25(50%)
Positive for H.pylori infection	3 (6%)	3 (6%)	6(12%)

Table – 5: Prevalence of patients with drug-induced UGI bleeding with respect to number of risk factors.

Number of risk factors	Male Patients (%)	Female Patients (%)	Total (%)
0	0	0	0 (0%)
1	1 (2%)	9 (18%)	10 (20%)
2	11 (22%)	5 (10%)	16 (32%)
3	7 (14%)	2 (4%)	9 (18%)
4	9 (18%)	2 (4%)	11 (22%)
5	2 (4%)	0 (0%)	2 (4%)
6	0 (0%)	1 (2%)	1 (2%)

Conclusion

The present study on drug-induced UGI bleeding concludes that Non-steroidal anti-inflammatory drugs were the causative drugs for UGI bleeding in all the fifty cases studied. Among the NSAIDs, prevalence of the causative drugs was as follows: Ibuprofen in 38% of cases, diclofenac in 28% and aspirin in 16%. All the fifty cases had at least one known risk factor and majority (80%) had more than one risk factors of drug induced UGI bleeding. The prevalence of risk factors was as follows: Age ≥ 50 years of age - 66%, 'O' Blood group – 50%, Alcoholism – 42%, Not using Gastro-protective agents – 40%, Self-medication / OTC drugs – 36%, Smoking – 30%, Stress and Serious systemic illnesses – 12%, Helicobacter pylori – 12%, Known Peptic ulcer disease – 10%, High doses/ Chronic drug intake – 10%, Concomitant use of Steroids – 8%, Concomitant use of Anticoagulants – 4%.

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