

Original Research Article

Pattern of drug-induced bleeding in a tertiary care hospital

Rajinder Negi¹, Rajesh Kashyap^{2*}, Anupam Prashar³, Brij Sharma⁴,
Sanjeev Asotra⁵, Dilip Gupta¹

¹Department of Medicine, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

²Department of Medicine and In charge Emergency, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

³Department of Preventive and Social Medicine, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

⁴Department of Gastroenterology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

⁵Department of Cardiology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

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*Correspondence:

Dr. Rajesh Kashyap,

E-mail: krajesh_shimla@yahoo.com

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ABSTRACT

Background: It is a well-known fact that drug-induced bleeding causes considerable morbidity and mortality. Drugs that induce bleeding do so by affecting either anti-platelet Function and /or coagulation. By the frequency of their use, anti-platelet, a coagulant, thrombolytic and NSAIDs are the most commonly implicated drugs. Upper gastrointestinal bleeding is commonest adverse drug reaction associated with hospital admission. Significant number of these could be prevented if simple guidelines are followed. Spontaneous cessation of bleeding occurs in as many as 85% of cases. Early intervention is required in those if bleeding does not stop spontaneously. Objective of the study was to determine the pattern of drug induced bleeding in tertiary care hospital setting.

Methods: It was a hospital based observational study conducted during one year study dura on ((June 1, 2014 to May 31, 2015) amongst all adult patients admitted to the hospital with drug induced bleeding. Statistical analysis was done by frequency measurement for categorical variables. Chi- square test was used to determine associations. A p-value of <0.05 was taken as statistically significant.

Results: A total number of 110 cases with history of bleeding were enrolled. Commonest drug that caused bleeding was a platelet with 29 (26%) cases followed by combination of 2 or more drugs in 25 (23%) cases, then NSAIDs and anticoagulants in 24 (21%) and 23 (20%) cases respectively. Upper gastrointestinal bleeding was the commonest site of bleeding seen in 64 (58%) cases. The commonest drugs causing upper GI bleeding were NSAIDs seen in 24 (37.5%) cases followed by a platelet 22 (34.3%), combined drugs in 09 (14%) cases. (P<0.001) In overall severity most cases of drug induced bleeding had mild bleeding with 61 cases as compared to 38 cases of moderate and 11 cases of severe bleeding. There were significantly higher proportion of mild and moderate bleeding in upper gastrointestinal bleed cases in comparison to other sites of drug induced bleeding in this study (p<0.01). 7 (6.4%) out of 110 patients died and 103 (93.6%) patients recovered and were discharged.

Conclusions: Clinical management of bleeds requires careful assessment of the patient, haemodynamic stabilisation, discontinuation of the offending medication and, where appropriate, reversal of the haemorrhagic effects and specific therapies such as endoscopic haemostatic therapy.

Keywords: Anticoagulants, Antiplatelets, Drug induced bleeding, NSAIDs, Severity of bleeding, Thrombolytics, Upper gastrointestinal bleed

INTRODUCTION

Drugs are the common cause of acquired bleeding disorder. In many cases the drug may be obvious, e.g. an anticoagulant but in other cases it may be less clear. In hospitalized patients, commonly used drugs causing bleeding are antiplatelet, NSAIDs, anticoagulants, thrombolytic, steroids and indigenous drugs etc.

In the recent past there has been increased use of drugs which can cause bleeding, better patient care, longevity of life and increased incidence of non-communicable diseases have led to increased use of antiplatelet and anti-thrombotic. However poor monitoring, uneducated patients, lack of precaution and failure on the part of physicians to properly educate the patients about the side effects due to the time constraints leads to increased incidence of bleeding in these patients. Incidence may be more in poor socioeconomic set up due to lack of education and lack of access to laboratory setup.

Non-steroidal anti-inflammatory drugs

NSAIDs are commonly used medications worldwide.¹ Most commonly used drugs are Aspirin, Ibuprofen, Diclofenac, Acenofelac, Nimuselide, Mefenemic acid and Indomethacin etc. About 30 to 50% of NSAIDs users have endoscopic lesions such as subepithelial haemorrhages, erosions, and ulcerations, mainly located in gastric antrum, and often without clinical manifestations.

Steroids are commonly used as anti-inflammatory, immunosuppressive and anti-allergic agent. Patients using steroids concomitantly with high dose NSAIDs has high risk of upper gastrointestinal complication.²

Antiplatelets

Commonly used oral antiplatelet agents are aspirin, clopidogrel, prasugrel etc and intravenous antiplatelet drugs are Abciximab and Eptifibatid etc.³ Incidence of aspirin induced bleeding accounts 2.7%.

Anticoagulants

Warfarin induced bleeding occurs in 1-5% of patients per year and has a case fatality rate of 25-30%.⁴

Thrombolytics

Common thrombolytic agents are Streptokinase, Urokinase, Alteplase, Tenecteplase and Reteplase and they are used in acute MI, acute ischaemic stroke and massive PE.⁵ Streptokinase is a common thrombolytic agent used in developing countries. Bleeding is major side effect of thrombolytic therapy and limits its usefulness. Heparin is common antithrombotic drug. The major side effect of heparin when administered therapeutically is bleeding.

Since the drugs are common cause of acquired bleeding disorder, this study was undertaken to know the pattern of drug induced bleeding amongst the patients in our centre and planning further strategies.

Objective of the study was to know the pattern of drug induced bleeding and to determine associated risk factors in a hospital setting.

METHODS

This was a hospital based prospective study, conducted over a period of one year (June 1, 2014 to May 31, 2015). All the adult patients with history of drug induced bleeding (anticoagulant, antiplatelet, thrombolytics, NSAIDs, steroids, indigenous medications etc.) admitted to casualty ward / medicine / cardiology ward / CCU / ICU / gastroenterology who consented to take part were enrolled in the study. Patients with history of traumatic bleeding, bleeding diathesis and who did not have history of drug induced bleeding were excluded from the study. All the enrolled patients were administered a pretested semi-structured questionnaire to determine the patient characteristics, history of drug intake, co-morbidities, length of stay and other relevant systemic examination and laboratory investigations. The patients were also subjected to Upper GI Endoscopy, Colonoscopy, CT/MRI brain, CT chest, Coagulation factor; if required

The severity of bleeding was classified into mild, moderate, and severe. Mild bleeding could be noted as petechial bleeding, mild blood loss (clinically significant) or bleeding not requiring transfusion; moderate bleeding could be noted as gross blood loss, requiring transfusion; and severe bleeding could be noted as debilitating blood loss, retinal or cerebral, associated with fatality. A written informed consent was taken from all the enrolled participants. The ethical approval was taken from the Institutional Ethics Committee prior to initiation of the study.

Statistical analysis

Frequencies with percentage were used to summarize age, sex, severity of bleeding, drugs involved in the bleeding, and comorbidities. The chi square test was applied as test of association. A 'p' value of <0.05 was considered statistically significant. The entire analysis was performed using SPSS version 20.0 (SPSS Inc. Chicago, USA).

RESULTS

A total number of 110 cases with history of bleeding were enrolled for the current study during one year study duration. There were 80 (72%) males and 30 (27%) females. Maximum incidence of bleeding by drug was seen in 6th decade which comprised 26.3% of total cases followed by 7th decade and 8th decade which comprised 20.9% and 19% respectively. Commonest drug that

caused bleeding was antiplatelets with 29 (26%) cases followed by combination of 2 or more drugs in 25 (23%) cases, then NSAIDs and anticoagulants in 24 (21%) and 23 (20%) cases respectively. Drugs like steroids and ayurvedic medicines were also implicated as cause of bleeding in 2 (1.8%) cases each (Table 1).

Table 1: Drug induced bleeding by type of drugs in the study population (n=110).

Drugs	No. of cases	Percentage
NSAIDs	24	21%
Antiplatelets	29	26 %
Anticoagulants	23	20%
Thrombolytics	05	04%
Steroids	02	1.8 %
Ayurvedic/ other drugs	02	1.8%
Combination	25	23%
Total	110	100%

The upper gastrointestinal bleeding was the commonest site of bleeding seen in 64 (58%) cases followed by bleeding through nose (epistaxis) and skin in 10 (09%) cases each, multiple sites in 8 (7.2%) cases, lungs in 6 (5.4%) cases and genitourinary in 5 (4.5%) cases. In 3 (2.7%) cases there was intracranial haemorrhage and one case each presented with bleeding through ear and knee joint.

Upper GI bleeding

Maximum patients with upper gastrointestinal bleeding were seen in age group of 51-60 years which comprised 18 (28.1%) cases, followed by 41-50 years with 13 (20.3%) cases. Out of 64 patients of upper gastrointestinal bleeding, 47 (73%) were males whereas 17 (27%) were females. The commonest drugs causing upper GI bleeding were NSAIDs seen in 24 (37.5%) cases followed by antiplatelets 22 (34.3%), combined drugs in 09 (14%) cases ($p < 0.001$) Table 2. Majority of the patients with upper gastrointestinal bleed presented with both hematemesis and melena with 27 (42.1%) patients followed by melena alone in 22 (34.3%) cases.

Table 2: Relationship of type of drug intake with upper GI bleed cases.

Drugs	Upper GI bleed cases	Total cases
NSAIDs	24	24
Antiplatelets	22	29
Anticoagulants	06	23
Thrombolytics	0	05
Steroid	01	02
Ayurvedic/other	02	02
Combined	09	25
Total	64	110

Chi square (for linear trend) value =23; p- value <0.001.

Gastric ulcers were most commonly associated with NSAIDs, whereas duodenal ulcers were mostly associated with antiplatelets. Anticoagulants and steroids caused superficial erosions. Single case of MWS was caused by antiplatelets. Out of 64 patients of upper GI bleed, PPI/Triple therapy was given to 61 (95%) patients, sclerotherapy was given to two patients and injection therapy was given to one patient. Blood transfusion of four or more units was required in five patients.

NSAIDs

NSAIDs were most commonly used in the age group between 41-60 years which comprised 12 (50%) cases. Diclofenac alone and in combination was commonest NSAID that induced bleeding in 17 (70%) cases. Musculoskeletal pain was most common indication for NSAIDs use in 9 (37.5%) cases.

Antiplatelet drugs

Commonest age group of antiplatelets induced bleeding was 51-60 years. Common indication of antiplatelets was coronary artery disease (19 cases). Comorbid medical conditions were associated in maximum cases. Commonest site of bleeding (76%) was upper gastrointestinal tract. Dual antiplatelets were prescribed more commonly than single drug.

Anticoagulant drugs

Anticoagulants were commonly used in the age group 61-70 years. Valve replacement/disorder (39.1%) was commonest indication of anticoagulant therapy. Commonest site was upper GI tract in 6 cases followed by skin in 5 cases. Comorbid conditions were present in 10 patients and 13 patients had no comorbidity. Majority of patients 17 (73%) had INR >4.

Thrombolytics

Thrombolytic induced bleeding was maximum in the age group of 71-80 years and in females. No case was seen in less than 50 years old. Indication for thrombolytics was ischemic stroke/CVA in all five patients. Intracranial haemorrhage was seen in 3 out of 5 cases.

Drugs in combinations

Combination of drugs was given in 25 patients out of total 110 cases. Maximum number of drug combination prescribed was anticoagulants with other drugs like NSAIDs, steroids and antiplatelets in 20 cases, four cases of thrombolytics combined with other drugs. Single case was of antiplatelet used in combination with NSAIDs.

Severity and outcome

In overall severity, most cases of drug induced bleeding had mild bleeding with 61 cases as compared to 38 cases

of moderate and 11 cases of severe bleeding. There were significantly higher proportion of mild and moderate bleeding in upper gastrointestinal bleed cases in

comparison to other sites of drug induced bleeding in this study ($p < 0.01$) (Table 3).

Table 3: Relationship of severity of bleeding with bleeding site.

Site	Severity			Total
	Mild	Moderate	Severe	
GIT	39	26	01	66
NOSE/EAR	06	04	01	11
Skin/ Soft tissue	09	01	01	11
CNS	-	-	05	05
Chest	03	02	01	06
Genito-urinary	03	02	-	05
Multiple/ sites	01	03	02	06
Total	61	38	11	110

Chi-square (for linear trend) value= 6.05; p-value<0.01

7 (6.4%) out of 110 patients died and 103 (93.6%) patients recovered and were discharged.

DISCUSSION

In total 110 cases were studied in duration of one year from 1st June, 2014 to 31st May, 2015 who presented with bleeding due to drug taken for various medical illnesses. The current study studied full spectrum of drug induced bleeding in comparison to other studies searched in the literature which mostly covered individual drug groups.

In the present study, maximum incidence of bleeding by drug was seen in 6th decade which comprised 26% of total cases followed by 7th decade and 8th decade which comprised 20% and 19% respectively. Similarly, older age was found to be risk factor in various studies on individual drug groups. Logan N et al in their studies of NSAID induced bleeding found most common age group of 6th to 7th decade respectively. Studies by Nekkanti H et al and Hollowell J et al on warfarin induced bleeding also found common age group of 6th decade and 8th decade respectively in their studies.⁷⁻⁹ Yasuda et al also found older age group to be a risk factor in study on antiplatelet induced bleeding.¹⁰

There was overall male predominance with 80 (72%) cases of males and 30 (27%) cases of females and M: F ratio of 2.7:1. Maximum numbers of patients with upper gastrointestinal bleeding were seen in 51-60 years' age group with male predominance in 73% cases. Similarly, Logan N et al also studied 88 cases of upper GI bleed and found 6th decade to be the commonest age group and male predominance with 51 (58%) cases.⁷

NSAIDs were the commonest drugs implicated for upper GI bleeding in our study with 24 (37.5%) cases. Logan N

et al also found that NSAIDs/Aspirin was most common drug causing upper GI bleed in 46 (52.3%) cases out of 88 cases. The patients on NSAIDs had significantly higher incidence of upper GI bleed as compared to patients on other drugs like anticoagulants, antiplatelets etc. (Table 2). In present study peptic ulcer was most frequent lesion in upper GI bleeding with 33 out of 64 cases. Study by Piper JM et al also showed that peptic ulcer is the most common cause of upper gastrointestinal bleeding (50% in older series, but around 33% in more recent ones).¹¹

In the present study NSAIDs were most commonly used in the age group between 41-60 years which comprised 12 (50%) cases. Similarly, Logan N found 7th decade and 6th decade respectively to be common age group for NSAIDs induced bleeding. There was greater number of males admitted with NSAIDs induced bleed which was like study conducted by Ishikawa S.¹² However, Logan N et al found females to have more NSAIDs induced bleeding as females in their study were more likely to use pain killers. In general, men have twice the risk for serious GI bleeding than women ref. Diclofenac alone and in combination with other NSAIDs or non-NSAIDs was most commonly implicated drug in NSAIDs induced bleeding in this study. Aspirin and diclofenac was commonest drug implicated in Upper GI bleed in a study conducted by N Logan. However Ishikawa S found Ioxoprofen followed by diclofenac as most implicated drugs for bleeding. This disparity may be due to the reason that Ioxoprofen is not commonly prescribed medicine in our institution.

In the present study, musculoskeletal pain was the most common indication for NSAIDs use in 09 out of 24 cases. However, Logan et al and Ishikawa S et al found that arthritis is the most common indication for NSAIDs use. This disparity could be explained by over the counter

usage of NSAIDs in musculoskeletal pain in our set up. Concomitant therapy of gastro protective agents such as proton pump inhibitors, H2 antagonist and prostaglandin analog were not used along with NSAIDs, which could reduce the occurrence of Upper GI haemorrhage.

Laine L et al found gastric ulcers are approximately four times more common than duodenal ulcer in patients taking NSAIDs.¹³ Present study also showed that gastric ulcer was more common than duodenal ulcer in patients taking NSAIDs.

Antiplatelet drugs

In the present study of 110 cases antiplatelet drug was commonest cause of bleeding, because antiplatelet therapy is widely used in primary and secondary prevention of coronary artery disease and ischaemic stroke. The commonest indication of antiplatelets in present study was coronary artery disease which was seen in 19 cases out of total 29 cases. Yasuda H et al also mentioned in their study that acute coronary syndrome is most common indication for antiplatelet drug use.¹⁰

Commonest site of antiplatelet drug induced bleeding was upper gastrointestinal tract with male preponderance and mean age 62 years. Inamulhaq et al found dual antiplatelet induced bleeding in patients with mean age 66 years, male 67% and female 37%.¹⁴ Yasuda H et al found antiplatelet therapy causes gastrointestinal bleeding in elderly patients.¹⁰ In a present study also patients with bleeding due to antiplatelets therapy were seen in 6th to 7th decade with male preponderance. Commonest site of bleeding was upper gastrointestinal tract which comprised 22 (76%) cases out of total 29 cases. Yashuda et al also found gastrointestinal bleeding is one of the most common complications of antiplatelet therapy.

Out of 29 cases, 15 patients were taking dual antiplatelets and rests 14 were taking single drug. Similarly, in a study by CURE combination of aspirin and clopidogrel increased the rate of major bleeding (3.7%) compared to aspirin alone (2.7%).¹⁵ In the present study majority of patients were taking dual antiplatelet which could be the reason of increased occurrence of bleeding. Proton pump inhibitors or H2RA were not prescribed along with antiplatelet therapy which could also reduce the risk.

Anticoagulant

Anticoagulant induced bleeding was most common in 61-70 years age group. The common age group in studies by Nekkanti et al and Hollowell J et al were 41-61 years and 70-79 years respectively.^{8,9} Out of 23 patients 16 (69.5%) were male and 07 (30.5%) were females. Similarly, Hollowell J et al found more incidences in male patients with 52.6% cases. However, Nekkanti H et al found more incidences in females with 62.2% cases. Valve replacement/disorder were commonest indications of anticoagulant therapy comparable to study by Hollowell J

et al with maximum incidence in valvular disorders. Commonest site of bleeding was upper GI tract which comprised 06 cases out of total 23 cases. Whereas Hollowell J et al found that genitourinary bleeding was most common site for anticoagulant bleeding.

In 23 cases of anticoagulant induced bleeding, comorbid conditions were present in 10 patients and 13 patients had no comorbidity. The most common comorbid condition was diabetes followed by hypertension and kidney disease. Nikkanti et al also found diabetes and hypertension as common comorbid conditions in 23 and 20 cases out of total 61 cases in warfarin induced bleeding. Out of 23 cases 15 cases had duration of drug intake for more than 6 months. Majority of patients 17 (73%) with anticoagulant drug induced bleeding had INR >4. Levine MN et al and Zareh M et al ref also studied that bleeding risk increases with INR >4, independent of indication of therapy.¹⁶

Thrombolytics

Thrombolytic induced bleeding was maximum in 71-80 years' age group and more in females. However, Kumolosasi E et al found in his study on thrombolytic agents that the thrombolytic induced bleeding was more common in male patients less than 45 years.¹⁷ The disparity may be due to smaller sample size in our study.

The indication of thrombolytics in present study was ischaemic stroke in all five patients. Intracranial haemorrhage was seen in 3 out of 5 cases, rest of the sites was seen in lungs and nose. However, Kumolosasi E et al found that gum bleeding was more common site for bleeding followed by genitourinary bleed. In four cases, thrombolytics were used with other drugs and in all cases indication was STEMI. Site of bleeding were UGI in two cases, epistaxis with genitourinary and skin in one case each. Bleeding was severe in combination of TNK, DAP and warfarin which was fatal. Whereas combination of TNK, DAP and heparin caused moderate UGI bleeding.

Drugs used in combination

Combination of drugs was given in 25 patients out of total 110 cases. Maximum number of drug combination prescribed was anticoagulants with other drugs in 20 cases. Four cases of thrombolytics combined with other drugs are mentioned above. Single case was of antiplatelet used in combination with NSAIDs. Ho LL studied interaction of antiplatelet and warfarin and concluded that combination increases risk of bleeding. Similarly, Musumba CO also mentioned in his study that drugs used in combination is a risk factor for bleeding.^{18,19}

Severity

Most cases of drug induced bleeding had mild bleeding with 61 cases as compared to 38 cases of moderate and

11 cases of severe bleeding. No literature was found to compare overall severity of drug induced bleeding.

Final outcome of patients

7 (6.4%) out of 110 patients died and 103 (93.6%) patients recovered and were discharged.

CONCLUSION

Clinical management of bleeds requires careful assessment of the patient, haemodynamic stabilization, discontinuation of the offending medication and, where appropriate, reversal of the haemorrhagic effects and specific therapies such as endoscopic hemostatic therapy. In addition, it is equally important to counsel the patients regarding side-effects of the drugs to decrease morbidity and mortality due to drug induced bleeding.

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