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Non-traumatic Haemorrhagic Adverse Events: A Cross-sectional Study in Emergency Departments

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Abstract

Objectives: The aims of this cross-sectional study were to describe the incidence of haemorrhages and adverse drug events related to different classes of drugs as cause of emergency department admission.

Methods: Adult patients (≥ 18 years) visiting two emergency departments of the University Hospital in Verona (Italy) over a twelve-month period in 2015-2016 were included. The study takes into consideration non-traumatic haemorrhages defined through an International Classification of Diseases, Clinical Modification (ICD-9 CM) diagnosis code and classified into five groups (cerebral haemorrhage, gastrointestinal bleeding, epistaxis, haematuria and other haemorrhages). Demographic data, clinical data and outcome of hospitalization were extrapolated from computerized medical records. Drugs were grouped into six categories and linked to the prescription data of the Verona population during the study period.

Results: Overall, 117,019 admissions to emergency departments related to 101,053 patients occurred. According to selection criteria, 1,614 admissions for bleeding, which concerned 1,391 patients (1.4% of the total patients, 59.6% male, 45.7% ≥ 75 years old) were analysed. Out of 1,391 patients, 873 had taken at least one drug (62.8%). Patients were admitted more frequently for epistaxis and gastrointestinal bleeding (27.5% and 23.9%, respectively), and the most reported drugs were antiplatelet (38.8% and 37.7%, respectively) followed by anticoagulants (23.5%), heparins (8.4%), corticosteroids (6.2%), SSRI (5.6%) and NSAIDs (3.0%). About 37% of the visiting patients were subsequently hospitalized, and death was the outcome in 4.2% of cases.

Conclusion: In emergency department about 1.4% of admitted patients had an haemorrhage, of these 37% have been hospitalized and 4.2% died during hospitalization. About one third of patients with haemorrhages did not use any drugs. The majority of hospitalized patients had gastrointestinal bleedings and cerebral haemorrhages. To the best of our knowledge, this study is new in the literature, since it takes into consideration all non-traumatic bleedings, and also all drugs known to be associated with haemorrhagic events mentioned on the clinical records.

Keywords: Haemorrhages; Bleeding; Emergency department; Adverse drug events; Observational study; Cross-sectional study; Gastrointestinal bleeding

Introduction

Non-traumatic haemorrhages are frequent clinical emergencies requiring urgent medical intervention; gastrointestinal and intracerebral ones are the most commonly encountered and challenging [1]. Acute Upper Gastrointestinal Bleeding (UGIB) is 60-90% more common than lower gastrointestinal bleeding [2], and it has an incidence ranging between approximately 50 and 150 per 100,000 inhabitants per year [3]. Often associated with drug use, it remains a common cause of visits to the emergency department (ED), with an estimated incidence of about 100 hospital admissions per 100,000 inhabitants [4].

The incidence of non-traumatic cerebral haemorrhage is 24.6 cases per 100,000 persons per year [5]; it is a serious medical emergency, representing 20% of all hospitalizations for stroke [6]: drug use is not considered among its main causes [7].

Data about the incidence of total haemorrhagic events in the ED are lacking in literature; most of the studies report emergency admissions for bleeding associated with specific drugs (e.g., anticoagulants, antiplatelet drugs) or apparatus [8-12]. There is a need to collect real-world data in clinical practice, especially because in last years several new direct oral anticoagulants (DOACs) have been approved, and the use of antiplatelet drugs is increasing.

This observational study was performed using computerized medical records from the EDs of the University Hospital in Verona. Our aims were to describe the incidence of haemorrhages and adverse drug events (ADEs) related to different classes of drugs as cause of ED

admission, the characteristics of patients, the kind of bleeding and the description of hospitalizations and intra-hospital deaths.

Methods

Setting and case selection

This observational study was performed among adult patients (≥ 18 years). Cases were identified in two EDs of the University Hospital of Verona, which covers a population of about 300,000 inhabitants. All patients accessing from 1 February 2015 to 31 July 2015 and from 1 February 2016 to 31 July 2016, having an International Classification of Diseases, Clinical Modification (ICD-9 CM-9th revision) code of discharge related to haemorrhage without concomitant diagnosis of trauma, were enrolled.

Data extraction

Data was extrapolated from the First Aid database, which contains evaluation at admission, medical history, concomitant pharmacological treatment, descriptive discharge diagnosis, its corresponding ICD-9 CM code and outcome (back to home, hospitalization and intra-hospital death). Patients were anonymised by assigning them an alphanumeric code (enterprise patient ID [EPID]), which was used by the Anag (containing demographic data) and

Opera (which included diagnosis of admission, discharge and outcome of hospitalization) databases. Drug prescription data of the Verona population during the study period was obtained from the administrative database of Local Health Service.

This study was conducted after the approval of the local ethics committee for human research in accordance with Italian law.

Definitions

Haemorrhage was defined through an ICD-9 CM diagnosis code for any minor or major bleeding, except for traumatic ones. The narrative sections of the charts were further reviewed case by case to augment data quality.

Case selection was done using the ICD-9 CM codes list made up by Pinto et al. [13]. Haemorrhages were classified into 5 groups: cerebral haemorrhage, gastrointestinal bleeding, epistaxis, haematuria and other haemorrhages (Supplementary Table 1). Drugs known to be associated with haemorrhagic events were grouped into six categories: anticoagulants, antiplatelet drugs, heparins, corticosteroids, selective serotonin re-uptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory drugs (NSAIDs), and we considered suspected haemorrhagic ADEs in all patient records reporting at least one of these drugs.

	Total N=1391(%)	Epistaxis N=383(%)	Gastrointestinal Hemorrhage N=332(%)	Hematuria N=317(%)	Cerebral Hemorrhage N=198(%)	Other Hemorrhage N=161(%)
Gender						
Male[*]	829 (59.6)	206 (53.8)	174 (52.4)	255 (80.4)	93 (47.0)	101 (62.7)
Female[*]	558 (40.1)	177 (46.2)	156 (47.0)	61 (19.2)	105 (53.0)	59 (36.6)
Age, years (mean ± SD)	69 ± 18	69 ± 18	68 ± 19	73 ± 15	68 ± 15	61 ± 20
Patients treated with at least one drug	873 (62.8)	245 (64.0)	231 (69.6)	215 (67.8)	92 (46.5)	90 (55.9)
Hospitalized patients	515 (37.0)	12 (3.1)	199 (59.9)	73 (23.0)	189 (95.5)	42 (26.1)
[*]Four patients with no indication of gender.						

Table 1: Baseline characteristics of patients with discharge diagnosis related to most common haemorrhage.

Statistical analysis

To estimate the incidence of hemorrhagic patients entering the emergency department during the study period we calculated the ratio between the patients with an ICD-9 DM diagnosis that code for a haemorrhage respect to all patients who entered in the same period. Descriptive baseline characteristics were expressed in percentages and means ± standard deviation of the mean. Data about hemorrhage and drugs are presented as percentage since they are categorical variables.

Results

The cumulative number of visits to the ED in the study period was 117,019 (101,053 patients), of which 1,614 had a diagnosis of haemorrhage without a concomitant diagnosis of trauma (corresponding to 1500 patients). Because 109 of these patients were excluded due to a diagnosis of traumatic bleeding identified in the medical records, 1,391 patients were included in the analysis (1.4%) (Figure 1).
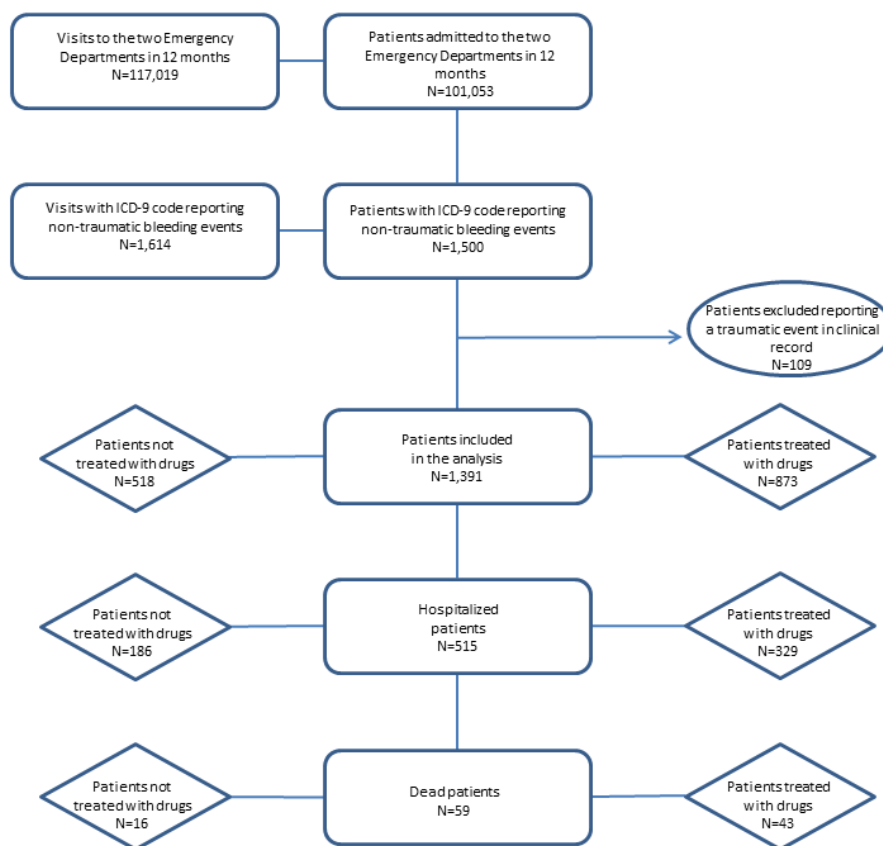
Figure 1: Flow diagram of visits and patients.

Table 1 shows the physical characteristics of this population with the related haemorrhagic adverse events. The most common haemorrhages were epistaxis (27.5% out of 1,391), followed by gastrointestinal bleeding (23.9%) and haematuria (22.8%).

Haemorrhages occurred in more males than females (59.6% versus 40.1%) both in general and when considering each group, with the exception of cerebral haemorrhage. Out of 1,391 patients, 873 took at least one drug (62.8%). The rate of drug assumption was about 70% for gastrointestinal bleeding and haematuria and lower for the others. Most of patients were over 75 years old (45.7%, Figure 2).

As reported in Table 2, the most used drugs before the patients' access to the EDs were antiplatelet drugs (36.9%, mainly acetylsalicylic acid 100 mg, 215 cases out of 322), followed by anticoagulants (23.5%), heparins (8.4%), corticosteroids (6.2%), SSRI (5.6%) and NSAIDs (3.0%). In particular, out of 205 patients treated with anti-coagulants, 181 used warfarin and 25 used DOACs. (One patient took both.) Epistaxis and gastrointestinal bleeding were the most frequent ADEs associated, respectively, with warfarin and DOACs. Cerebral haemorrhages were absent in DOAC users, whereas they reached 9% with warfarin. Out of 26 NSAIDs users with any kind of bleeding, the most frequent was gastrointestinal haemorrhage, with 14 cases. Table 3 shows the prescriptions of anticoagulant and antiplatelet drugs of

Verona inhabitants in the study period. Warfarin presents a higher percentage of bleedings than DOACs (1.85 *vs.* 0.95), and aspirin or clopidogrel monotherapy has a lower percentage than the combination has (0.92 and 1.12, respectively, *vs.* 1.44).
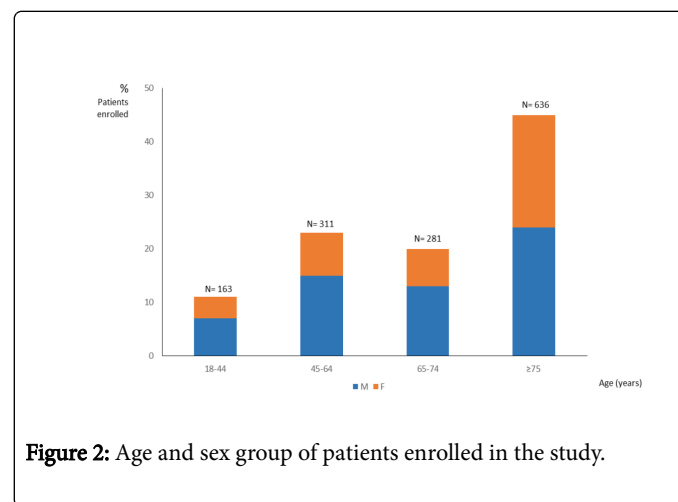

Figure 2: Age and sex group of patients enrolled in the study.

Drug category	Epixtasis N=245 (%)	Gastrointestinal Haemorrhage N=231 (%)	Hematuria N=215 (%)	Cerebral Haemorrhage N=92 (%)	Other Haemorrhage N=90 (%)	Total N=873 (%)
Antiplatelet drugs	95 (38.8)	87 (37.7)	73 (34.0)	39 (42.4)	28 (31.1)	322 (36.9)
Anticoagulants	78 (31.8)	38 (16.5)	43 (20.0)	16 (17.4)	30 (33.3)	205 (23.5)
Heparin	7 (2.9)	20 (8.7)	28 (13.0)	6 (6.5)	12 (13.3)	73 (8.4)
Corticosteroids	9 (3.7)	15 (6.5)	16 (7.4)	4 (4.3)	10 (11.1)	54 (6.2)
SSRI	5 (2.0)	19 (8.2)	16 (7.4)	5 (5.4)	4 (4.4)	49 (5.6)
NSAIDs	5 (2.0)	14 (6.1)	3 (1.4)	2 (2.2)	2 (2.2)	26 (3.0)
Other	64 (26.1)	72 (31.2)	67 (31.2)	30 (32.6)	22 (24.4)	255 (29.2)

*The total number of patients treated with the analyzed drugs is not 873 because of possible multitherapy.

Table 2: Patients treated with at least one drug subdivided by drug categories and haemorrhagic events.

In total, 515 (37.0%) patients were hospitalized (Table 4). Three hundred and twenty-nine hospitalized patients were treated with at least one drug (63.9%), males more than females (277 versus 237), and the mean age was slightly higher than total cases (71 ± 16 versus 69 ± 18). In these patients, the more frequent haemorrhages were gastrointestinal bleeding (38.6%), followed by cerebral haemorrhage (36.7%). The rate of hospital admission was very different among groups. In the epistaxis group, 3.1% was hospitalized, and the outcome was death in one case, whereas 95.5% of patients with cerebral haemorrhage were hospitalized, and 23.2% died. The 59 (4.2% of 1,391) patients who died during the hospital stay were older than 76 (± 12) years, in majority women and admitted mainly for cerebral haemorrhage (46 cases).

Drug	Verona citizens on at least one prescription drug	Patients with bleeding events	%
Anti-coagulants			
Warfarin	9757	181	1.85
DOACs (dabigatran, rivaroxaban, apixaban)	2627	25	0.95
Anti-platelets			
Acetylsalicylic acid	25486	235	0.92
Ticlopidine	4418	23	0.52
Clopidogrel	2319	27	1.12
Double antiplatelet therapy*	1932	28	1.44

*Association of acetylsalicylic acid with clopidogrel.

Table 3: Incidence of haemorrhagic events diagnosed in EDs related to Verona citizens' drug prescription data in the same period.

Discussion

To the best of our knowledge, this study is new in the literature, since it takes into consideration all non-traumatic bleedings, and also all drugs known to be associated with haemorrhagic events mentioned on the clinical records. In our study, about 1.4% of the patients visiting the considered EDs had a haemorrhage; a majority had epistaxis and gastrointestinal bleedings. About one-third of the patients had not used any drugs before the haemorrhagic event occurred. About 37% of visiting patients were subsequently hospitalized, and death was the outcome in 4.2% of cases. The focus on haemorrhages in the ED is relevant. Budnitz et al. analyzing data from 58 non-paediatric hospitals in the United States, reported that among adults ≥ 65 years old, 73% of ED visits for ADEs caused by warfarin resulted in haemorrhage [8]. In another article on the same sample, they estimated that 45% of first-aid visits caused by haematologic agents (warfarin, antiplatelet drugs) resulted in hospitalization, especially for acute haemorrhages [9]. In our study, 1.4% of patients accessing EDs reported a bleeding event. A slightly higher result was found by Conti et al. (1.8% out of 166,000 visits) [14], probably because they did not exclude traumatic haemorrhages. Our research focused on non-traumatic bleedings, because we were not interested in the effects of drugs on bleeding complications in trauma patients. All haemorrhagic events were analysed, regardless of the drug used and the relationship between drug and event, contrary to Budnitz et al., who first identified the drug use and, successively, the possible haemorrhagic event [8].

Our mean age of cases was lower than that reported by Bouget [15] and Budnitz [8] (69 years old versus 82 and 77–79 respectively), probably because our study collected data related to all bleedings, whereas Bouget et al. [15] concentrated only on the major haemorrhages associated with antithrombotics, which is a drug class frequently used by older people. The study by Budnitz et al., instead, enrolled only adults aged ≥ 65 [8].

In general, there is a prevalence of bleeding occurrence in male patients (59.6%), in particular regarding haematuria (80.4%). This might be caused by the frequency of prostate-related diseases.

Haemorrhages occurred prevalently in male patients with the exception of the cerebral haemorrhage group.

When we divided the haemorrhagic adverse events in groups, epistaxis was the more frequent kind of bleeding (383 out of 1,391, 27.5%), followed by gastrointestinal bleeding and haematuria (23.9 and 22.8%, respectively). In contrast to our observations, Conti et al. reported that the most frequent bleedings were gastrointestinal (22%), intracranial (21%), haematuria (19%) and epistaxis (18%), [14]. On the other hand, Pallin et al. who investigated the epidemiology of epistaxis in U.S. EDs from 1992 to 2001, reported epistaxis as a common reason for emergency department attendance, accounting for up to 1 in 200 ED visits. This result is closer to our data (489 visits for epistaxis, 1 in 239 ED visits) [16].

	Total N	Discharged from hospital N (%)	Died during the hospitalization N (%)
Number of patients (%)	515	456 (88.5)	59 (11.5)
Gender			
Male*	277	254 (91.7)	23 (8.3)
Female*	237	201 (84.8)	36 (15.2)
Age, years (mean ± SD)	71 ± 16	71 ± 16	76 ± 12
Patients treated with at least one drug	329	286 (86.9)	43 (13.1)
Type of hemorrhage			
Gastrointestinal hemorrhage	199	191 (96.0)	8 (4.0)
Cerebral hemorrhage	189	143 (75.7)	46 (24.3)
Hematuria	73	70 (95.9)	3 (4.1)
Epistaxis	12	11 (91.7)	1 (8.3)
Other hemorrhage	42	41 (97.6)	1 (2.4)
*1 patient with no indication of gender.			

Table 4: Characteristics of patients hospitalized after ED visit.

As in Conti et al. [14], also in our study the most frequently involved drugs were antiplatelet, followed by anticoagulants, which reflects their wide use in the real world. Surprisingly, only a few haemorrhages were related to nonsteroidal anti-inflammatory drugs. This may be caused by the lack of attention given to over-the-counter drugs by both clinicians and patients, who fail to mention them when filling in the drug history records.

In our analysis, warfarin caused more bleeding events than DOACs (1.85% vs. 0.95%), which is consistent with a previous systematic review in which target-specific oral anticoagulants were associated with lower risks of major bleeding and any bleeding in comparison with vitamin K-antagonists [17]. As in other articles, we too found that aspirin or clopidogrel monotherapy caused a lower percentage of haemorrhages than the dual antiplatelet therapy. As a matter of fact, a previous meta-analysis, including all vascular risk patients, concluded that compared with aspirin alone, dual antiplatelet therapy reduces the risk of stroke, though significantly increases the risk of major bleeding [18]. Because our prescription data does not take into consideration

acetylsalicylic acid, which might be purchased over the counter (given its low cost), the percentage of patients with bleeding events caused by it might be even lower. Ticlopidine is well known for being linked in particular to haematologic adverse events and in fact caused few haemorrhages. In our study, epistaxis was the less serious; as a matter of fact, its frequency of hospital admission was 3.1%, and the outcome was death in one out of 383 cases. Sethy et al., in a recent article characterizing patients with epistaxis accessing ED, concluded that out of 1,234,267 ED visits, the majority of patients were discharged home (95.5%) [19]. Cerebral haemorrhage was instead the most serious haemorrhagic event, with 95.5% hospital admissions and an association with the highest rate of deaths (46 in 198, 23.2%). In addition, Conti et al. stated that intracranial haemorrhage was more likely to be associated with the highest rate of mortality [14].

Limitations and Strengths

In our study, a relevant number of ED visits (1,614) and patients (1,500) were collected consecutively. Medical and pharmacologic history of patients, discharge diagnoses and visit outcomes were registered on clinical electronic records by trained and qualified physicians. A case-by-case assessment evaluation was performed by a skilled data manager to set up a database excluding traumatic reports. Furthermore, the narrative sections of the charts were reviewed to verify the overlap between the ICD-9 CM diagnosis codes and the text description of the hemorrhagic event. Subsequently, the data manager entered the drugs of each medical record into the specific categories, therefore allowing the divergent terminology used in the charts to become univocal.

However, our work presents some limitations. First, because our reference population was inhabitants of the city of Verona, our results cannot be automatically generalized to other populations. Furthermore, our data did not include information about patient behaviour (e.g., smoking habit, alcohol use, drug abuse, etc.), clinical examinations and therapies performed in the ED that might have affected the etiology of bleedings. Despite the quality of the health professionals, the urgent character of emergency situations, the shortage of time and the lack of a specific questionnaire may have hindered the collection of medical history information, especially about drug use. However, this limit could have affected only data about drug use and not those about haemorrhagic diagnoses.

The fact that non-Verona citizens might access our study EDs should be counterbalanced by the possibility for Verona citizens to visit other EDs in the area as well, and the numeric difference, therefore, should not be relevant.

Conclusion

Our study presents a real-world scenario of emergency admissions for bleeding events at the two EDs of the University Hospital of Verona.

Haemorrages are more frequent in older people (45.7% more than 75 years old); 37.0% of patients with haemorrages have been hospitalized. Patients presenting cerebral haemorrhage have been hospitalized in 95.5% of cases and 23.2 died during hospitalization. Older age, female gender and cerebral hemorrages have been more associated with death.

The already relevant role of drugs (two-third of patients had used them) might have been underestimated, due to the uncertain accuracy in gathering the pharmacological anamnesis. Patients principally resorted to the emergency departments for not serious epistaxis.

Conflicts of Interest and Source of Funding

Acknowledgements

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