Original Article:

Hemorrhagic Events in Patients Receiving Heparin or Enoxaparin in Combination With Oral Antithrombotics, NSAIDs, and Antiplatelet Medications: A Multi-Center Case-Series Study

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ABSTRACT

Background: Hemorrhagic events are amongst the significant adverse effects of injectable anticoagulants such as heparin and enoxaparin. This undesirable effect needs close monitoring of their use for clinically relevant drug-drug interactions.

Objectives: To study the rate of hemorrhagic events, the anatomical site, and the severity of the bleeding in patients receiving heparin or enoxaparin in combination with clopidogrel, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and warfarin.

Methods: We designed a prospective, multi-center, case-series study. Patients admitted to two teaching hospitals who received either an NSAID, or warfarin, or clopidogrel were evaluated. Any hemorrhagic event was recorded by Yellow Card Scheme. Also, the Naranjo scale was utilized for causality assessment.

Results: A total of 123 patients were eligible for inclusion. They were admitted between November 2014 and April 2015. Sixty-five patients (52.5%) received heparin and 58 patients (47.2%) received enoxaparin. Of 123 patients, 115 patients (93.5%) received aspirin, 69 (56.1%) warfarin, 34 (27.6%) an antiplatelet medication, and 121 (98.4%) NSAIDs in combination with heparin or enoxaparin. Overall, 26 cases (21.1%) of the hemorrhagic incident were reported, of whom six cases (4.9%) were categorized as major bleeding. Patients receiving heparin constituted the largest proportion among all 26 hemorrhagic incidents (57.7%). All patients with the hemorrhagic incident had aspirin in their medication regimen, while 19 patients (73.0%) were concomitantly receiving warfarin as well. Hematuria (46.2%), hematoma in the injection site (38.5%), and hematoma (34.6%) were the top three types of hemorrhagic events. In Naranjo scale analysis, 19 patients scored more than 9 points, indicating a definite Adverse Drug Reaction (ADR) causality. Moreover, seven patients scored 5 to 8, affirming a possible association with ADR.

Conclusion: The risk of hemorrhagic can be influenced by undesirable drug-drug interactions. Close monitoring of high-risk patients is advised to prevent adverse hemorrhagic reactions. Further studies to detect the explanatory factors associated with the hemorrhagic events are recommended.

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Introduction

Hemorrhage is the most common complication associated with anticoagulant therapy [1]. Therefore, treatment with anticoagulant medications requires accurate dosing and appropriate monitoring as well as continuous patient education. The risk of bleeding in patients on anticoagulant therapy depends on various factors such as the duration of treatment, concomitant use of medications, history of Gastrointestinal (GI) bleeding or stroke, and liver or renal failure [1-4].

Depending on the coexisting risk factors, all hospitalized patients at risk for Venous Thromboembolism (VTE) should receive an appropriate prophylactic anticoagulant regimen. This regimen should be continued as long as the risk factors are present [1, 5, 6].

There has been an increase in the rate of heparin and enoxaparin use in the past decade. Global reports indicate an annual growth of 10%-15% in heparin use, which necessitates up-to-date programs to scrutinize the safety of prescribing and administration of heparin and enoxaparin to patients [3]. Monitoring Adverse Drug Reactions (ADRs) and potential complications related to coadministration with other medications is particularly important in patients receiving anticoagulant treatment [3]. When performed effectively, monitoring can benefit patients in different ways leading to the selection of the optimum drug regimen, improved patient outcomes, and prevention of ADRs [3, 7].

Although drug therapy monitoring to detect potential ADRs has remained a crucial part of a patient's rationale pharmacotherapy process, enough attention has not been paid to implement and improve ADR monitoring strategies. Suboptimal practice around the safety and efficacy monitoring for heparin use has been shown where 22% of patients receiving heparin have experienced an ADR, with 7% of the patients showing coagulation abnormalities [3].

Several descriptive reports in the hospital settings relate to the incidence of hemorrhagic events with heparin and enoxaparin use [3, 8-11]. In a study among hospitalized patients with chronic kidney dysfunction, 33% of patients receiving anticoagulation experienced significant bleeding. In particular, patients who were treated with unfractionated heparin had a higher risk of major bleeding compared to those who received enoxaparin [7]. Another study on the safety of heparin use combined with antithrombotic medicines, warfarin, and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) showed coagulation abnormalities among 7.4% of the patients [3]. Coadministration of heparin with these medications was associated with an increased risk of adverse drug reactions [3].

As our bibliographic search revealed, studies focusing on the safety of heparin and enoxaparin use and related issues, mainly when they are administered in combination with other medications, are scarce. Therefore, we aimed to investigate the risk of coadministration of oral antithrombotic, antiplatelet medications, and NSAIDs on heparin and enoxaparin safety. More specifically, this study is focused on the frequency of hemorrhagic events during the concomitant use of these medications in hospitalized patients and the types of the hemorrhagic events based on the anatomical site and severity of the bleeding.

Materials and Methods

The research was designed as a prospective, multi-center, descriptive, observational, case-series study in Masih Daneshvari Hospital and Shahid Rajaei Heart Center. These two centers were affiliated with Tehran University in Tehran City, Iran. The study was conducted for six months, from November 2014 to April 2015. Ethical approval was obtained from the hospital ethics committees before the commencement of the study.

Patients who started receiving either heparin or enoxaparin combined with at least one oral anticoagulant medication, NSAID, or antiplatelet medication during the study period were included in the study. A pre-designed data gathering form was used to collect the relevant information. Moreover, an adverse effect reporting form (Yellow Card) was filled for all observed hemorrhagic events. Details about the combination therapy of anticoagulants, antiplatelets, and NSAIDs with heparin and enoxaparin, including the name of medications, duration of therapy, and the duration of concomitant use, were retrieved from the patients' medical charts and kardexes. Patients' demographics, duration of hospitalization, comorbidities, and medication history of the patients were recorded, too. Laboratory data, including platelet count, hemoglobin (Hb) level, and International Normalized Ratio (INR), were also obtained from patients' records. If a patient with platelet counts below the normal range (<150000/µL), Hb value below 4 mg/dL and INR more than 4 units were identified, the responsible nurse was notified, and the patient was monitored closely for the possibility of hemorrhagic events [3, 12].

Patients were monitored for developing any hemorrhagic event during their treatment until they were discharged from the hospital. The site of bleeding and the

incidences of major hemorrhage were recorded for all hemorrhagic events. In terms of the bleeding site, hemorrhage can be categorized based on different body systems and organs, including Gastrointestinal (GI) hemorrhage, epidural hematoma, groin hematoma, respiratory tract bleeding, adrenal, intraocular and intracranial hemorrhage, rhinorrhea, and gingival bleeding, or any other organ bleeding [3, 12].

Major bleeding was defined as clinically excessive loss of blood which manifests itself as intracranial bleeding, groin hematoma, gastrointestinal bleeding, or retroperitoneal bleeding accompanied by a critical decline in the patient's hemoglobin levels for less than 4 g/dL [3, 12]. To evaluate the association of adverse drug reactions with the study medications, we assessed the adverse reactions using a scoring system of the Naranjo scale [13].

Data were presented descriptively as frequency and percentage of the outcome events, and also statistical analyses were applied for comparative purposes, where applicable. In this regard, the Chi-square and Mann-Whitney U tests were used by applying the SPSS software, version 22. Associations with a P-value less than 0.05 were considered statistically significant.

Results

One hundred and twenty-three patients hospitalized in the Shahid Rajaee Heart and Cardiovascular Diseases Center and Masih Daneshvari Hospital were entered into the study. The Mean±SD age of the patients was 58.25±14.07 years, and 40.65% (n=73) of them were females. Demographic information of patients is presented in Table 1.

The medical and medication history of the patients showed that hypertension (56.53%), diabetes (28.45%), and dyslipidemia (26.01%) were the three main comorbidities among the patients. Two significant indications for the prescription of anticoagulant agents in these patients were coronary artery bypass surgery (n=79; 64.22%) followed by mitral valve replacement (n=19; 15.44%). Other indications were stroke (4.06%), myocardial infarction (3.25%), coronary angioplasty (3.25%), and deep vein thrombosis (2.43%). The details of the indications for anticoagulant administration are summarized in Table 2.

In terms of anticoagulant use, 65 patients (52.84%) received heparin, while 58 patients (47.16%) received enoxaparin during the study period. Among concomitantly prescribed medicines, NSAIDs were the most commonly prescribed group (98.37%). Aspirin had the highest rate of prescription among the NSAIDs with 115 (93.49%) instances. This order was followed by warfarin and antiplatelet agents (e.g. clopidogrel) prescribed in 69 (56.09%) and 34 cases (27.64%), respectively.

During the study period, 26 patients (21.13%) developed hemorrhage. Of these, six patients (4.87%) were presented with major hemorrhagic events. Four patients died during the study period, all of whom showed hemorrhagic signs. Two of the deceased patients had significant bleeding. The symptoms and sites of hemorrhagic events differed among patients. Table 3 presents the symptoms and sites of hemorrhage in more detail.

Seven patients were found to have an INR> 4, of whom six patients (85.7%) experienced a hemorrhagic incident. All patients with the hemorrhagic incident had aspirin in their medication regimen, while 19 (73.0%) patients were concomitantly receiving warfarin as well.

According to the Naranjo scale, 19 patients scored more than 9 points, indicating a "definite" ADR causality. Moreover, seven patients scored 5 to 8, affirming a "probable" association with ADR.

As secondary outcomes, no statistically significant association was found between the occurrence of bleeding with the age of the patients and the duration of treatment

Table 1. Demographic information of the study patients

Variable	Mean±SD / No.(%)
Age, y	58.3±14.1
Female:Male ratio, Value/Frequency	73:50
Duration of hospitalization, d	13.7±8.6
Duration of heparin/enoxaparin use with other study medications, d	13.3±8.5
Smoking or other substance use	24 (19.5)

PBR

Table 2. Indications of anticoagulant agents

Indication	No. (%)
Coronary artery bypass	79 (64.3)
Mitral valve replacement	19 (15.5)
Stroke	5 (4.1)
Myocardial infarction	4 (3.2)
Coronary artery angioplasty	4 (3.2)
Deep vein thrombosis	3 (2.4)
Other	9 (7.3)
Total	123 (100)

PBR

with heparin or enoxaparin (P=0.74 and P=0.60, respectively). Similarly, the association between the patient gender and the occurrence of bleeding was not statistically significant (P=0.12).

Discussion

The study findings showed that hemorrhagic events commonly occur in patients receiving heparin or enoxaparin anticoagulation combined with oral antithrombotics, NSAIDs, and antiplatelet medications. Some patients experienced major hemorrhagic events with the potential to severe consequent health complications or even death. These adverse drug effects may increase the burden of diseases. Several studies have previously looked at the incidence rate of hemorrhagic events in patients who receive combined antithrombotic and anticoagulant therapies, with the incidence of major hemorrhagic events ranging from 2% to 10% of the study populations [7, 12].

An INR value of more than 4 can increase the risk of bleeding [2]. In the present study, six of seven patients (85.7%) presenting with an INR higher than 4, experienced hemorrhage.

The final analysis of our data did not show a significant association between the age of the patients and the occurrence of hemorrhage, which was in accordance with findings of a previous study [3]. One explanation for this finding would be the longer duration of the concomitant

Table 3. Types of observed hemorrhagic events during the study period

Type of Hemorrhage	No. (%)
Hematuria	12 (46.2)
Hematoma in the injection site	10 (38.5)
Hematoma (other than injection site)	9 (34.6)
Ecchymosis	7 (26.9)
Surgery site hemorrhage	7 (26.9)
Respiratory tract hemorrhage	4 (15.4)
GI bleeding	4 (15.4)
Groin hematoma	2 (7.7)
Retroperitoneal bleeding	2 (7.7)
Gingival hemorrhage	1 (3.9)

PBR

treatment with heparin and other study medications in this study, compared to similar studies [3, 7]. In other words, prolonged exposure to the combination of these medications may have made the patients more susceptible to develop hemorrhagic events regardless of their age. The Mean±SD duration of the heparin or enoxaparin coadministration with other study medications was 13.33±8.51 days in this research which was considerably longer than 3.5-4.3 days in similar studies [3, 7].

The incidence of hemorrhagic events was relatively higher in this study, with more than 20% of patients being affected. This may be due to the differences in guidelines applied to monitor therapy and how strict they are implemented in various study settings. Moreover, the results may be influenced by population and patient characteristics. For instance, patients with VKORC1 genetic polymorphisms have shown to demonstrate highly varying responses to anticoagulant therapies, which may increase the risk of bleeding in these patients [14]. In a previous report in 2008 at Masih Daneshvari Hospital, the prevalence of hemorrhagic events was reported above 9% [15]. The increase in the rate of hemorrhagic events in this study can be attributed to the increased rate of enoxaparin administration to the hospitalized patients in this center accompanied by the increased duration of coadministration with other studied medications shown by unpublished reports and self-experience of the authors. Furthermore, dose adjustments based on the present risk factors or other comorbidities may have been overlooked which consequently led to the increased rate of adverse events. The prevalence of hemorrhagic events, especially major bleeding, was notably higher in one study in patients with renal dysfunction, where one in every three patients experienced significant bleeding [7]. The possible mechanism behind this increased rate was explained by the critical role that the kidneys play in eliminating enoxaparin from the body.

Close monitoring of the patients can reduce the likelihood of developing adverse reactions. INR monitoring and making the required dose adjustments accordingly are crucial in preventing these events. Pharmacists can play their unique role in this regard by providing monitoring services, tailored patient assessment, and consultation, along with recommending necessary dose adjustments [16]. A previous study showed that clinical pharmacist-managed anticoagulation clinics improve anticoagulation control and optimize the safety of the treatment [16]. Clinicians ought to consider the individual characteristics of each patient and their comorbidities before any attempt to prescribe and administer these medications. Moreover, the significant drug-drug interactions with other concomitantly prescribed medications can further compromise the anticoagulant therapy outcomes and have the potential to increase the risk of hemorrhage.

This study was subject to some limitations. It is recommended that future studies with a larger sample size should be conducted. Moreover, missing laboratory data and the information about the type and bleeding site limited conducting more comprehensive statistical analyses.

Conclusion

Hemorrhagic events are significant complications that may result from anticoagulant therapy. The study findings showed that hemorrhagic events and especially major hemorrhagic incidents occur with a relatively high incidence in inpatients receiving heparin or enoxaparin therapy combined with oral antithrombotics, NSAIDs, and antiplatelet medications. Although no association was found between the age, sex, and the duration of treatment, it appears that concomitant prescribed medications can influence the risk of hemorrhagic events due to possible drug interactions. Patients should be thoroughly evaluated for their risk factors, concomitant prescribed and used medications, and coexisting medical conditions to attain an optimum anticoagulant regimen. A well-designed prospective cohort or case-control study can better identify the potential explanatory risk factors for hemorrhagic events.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization, writing – review & editing: All authors; Methodology: Fanak Fahimi, Jamshid Salamzadeh; Investigation, Fanak Fahimi, Amirhossein Ghanbarzamani, Jamshid Salamzadeh; Writing – original draft: Fanak Fahimi, Amirhossein Ghanbarzamani, Aida Sefidani Forough; Resources, Amirhossein Ghanbarzamani,

Conflict of interest

The authors declared no conflict of interest.

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