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DETECTION OF ADVERSE DRUG REACTIONS RELATED TO ANTICOAGULANT THERAPY IN HOSPITALIZED COVID-19 PATIENTS IN A TERTIARY CARE HOSPITAL IN KASHMIR, INDIA: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Coagulopathy is a potentially fatal complication of the newly discovered SARS-CoV-2 that significantly affects the hematological and hemostatic systems. Initial studies in COVID-19 patients reported lower mortality rates associated with the use of heparin. The most common adverse event related to anticoagulant therapy is bleeding. Low Molecular Weight Heparin (LMWH) is associated with less bleeding than Unfractionated Heparin (UFH). **Materials and Methods:** A prospective observational study was conducted at Chest Disease Hospital, Government Medical College, Srinagar over one year to assess the adverse drug reactions related to anticoagulant therapy in hospitalized COVID-19 patients. Data were collected using a suspected adverse drug reaction form (SADR) and then analyzed using appropriate statistical methods. **Results:** A total number of 225 patients were included in the study. In our study, 64% were male and 36% were female patients. A total of 5 different anticoagulant-associated ADRs were reported in 67 patients. The most common anticoagulant-related ADRs reported were bruises and areas of induration after subcutaneous heparin injection. **Conclusions:** As a result of heparin's wide range of biological activities, all of its undesirable effects are related to them. Bleeding is the most critical safety problem, directly resulting from its potency as an anticoagulant. Thrombocytopenia is the most severe nonbleeding adverse reaction caused by heparin.

KEYWORDS: COVID-19, SARS-CoV-2, Anticoagulants, Heparin, Adverse drug reaction, Coagulopathy.

INTRODUCTION

In the search for enhanced efficacy, it is vital to ensure the adequate safety of medicines.[1] However, in the face of a pandemic of such magnitude without a definitive treatment, the occurrence of adverse events in patients with COVID-19 is inevitably unpredictable. In COVID-19, anticoagulant therapy has been suggested as a mitigating strategy. However, there has been limited research on the adverse effects of anticoagulants in patients with COVID-19. The most common complication of anticoagulant treatment is bleeding. Low molecular weight heparin (LMWH) is associated with less severe bleeding than unfractionated heparin (UFH).[2] Heparin-induced thrombocytopenia (HIT) (platelet count <150,000/mL or a 50 percent decrease from the pretreatment value) occurs in 3 to 5 percent of patients receiving intravenous unfractionated heparin, compared with a 0.5 percent incidence with subcutaneous LMWH. Heparin-induced skin lesions at the site of subcutaneous injection and various systemic reactions may accompany HIT.[3] Heparin-related osteopenia and osteoporosis are rare but potentially serious complications of heparin and LMWH therapy. A rarely reported side effect of heparin is hyperkalemia, which occurs within a few days of starting treatment. It can affect the adrenal gland's capability to synthesize aldosterone and occasionally cause hyperkalemia.[4]

METHODOLOGY

This prospective observational study was conducted over one year from November 2021 to November 2022 at Chest Disease Hospital, Government Medical College, Srinagar after obtaining approval from the Institutional Ethics Committee. The current study was conducted by enrolling 225 hospitalized patients with a confirmed diagnosis of COVID-19. Patients of both sexes and over 18 years of age and prescribed anticoagulant therapy for further treatment during the hospital days.

Exclusion criteria

1. Patients who had an acute cardiovascular event in the last three months.
2. Patients who had an acute stroke (ischemic) in the last three months.

3. Patients with a history of active major bleeding.
4. Patients with a history of allergy to enoxaparin, components of heparin products, or heparin-induced thrombocytopenia (HIT).

The causality assessment of all suspected ADRs was completed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system.[5] The relationship was categorized as certain, probable, possible, unlikely, unclassified/conditional, or unclassifiable, and only ADR cases categorized as certain, probable, and possible were further analyzed. ADR severity was determined using the Modified Hartwig and Siegel Scale (1992).[6] Data analysis was completed using appropriate statistical methods.

RESULTS

A total of 225 patients were included in this study of which 64% were male and 36% female. The age of the patients in the study varied between 24 and 93 years. The mean age of the patients was 61.83 years with a standard deviation of 15.28 years. Out of a total of 225 patients, 67 patients (29.7%) had ADRs causally related to anticoagulant therapy. The most common anticoagulant-related ADRs reported were bruises and areas of induration after subcutaneous heparin injection in 59.7% (n=40) patients, heparin-induced thrombocytopenia [HIT] in 13.4% (n=9), headache in 13.4% (n=9), bleeding 9% (n=6) and hyperkalemia 4.5% (n=3). 61 ADRs (91%) were categorized as having a 'possible' causal relationship with anticoagulant therapy while six (9%) were categorized as 'probable' as per the WHO-UMC Scale. 91% (n=61) of ADRs were mild in severity as per the modified Hartwig and Siegel scale. Only 9% (n=6) of ADRs were moderate in severity.

There was a statistically significant relationship between the development of anticoagulation-associated ADRs and the age of the patient (P-value of 0.03), sex of the patient (P-value of 0.007), and comorbidity (P-value of 0.004) ADRs were most common in the age group of 61-80 years (66.1%) and least common in the age group of 21-40 years (25%). ADRs attributed to anticoagulant therapy were reported in 70.5% of females as compared to 45.6% of males. ADRs were present in 62.5% of the patients with underlying comorbidity.

DISCUSSION

Studies done early in 2020 by Tang et al. and Ayerbe et al. suggested that heparin may provide therapeutic benefits to COVID-19 patients.[7,8] Given the increased interest in anticoagulants such as heparin for use as a therapy for COVID-19, it seems extremely important to look at any adverse drug events arising from the use of this class of drugs. It has been established that the elderly population is more prone to developing ADRs.[9] Our study has shown that the risk of ADR increases by 1% with each increasing year of age. Older patients could be affected due to the presence of chronic disease, polypharmacy, and age-related physiological changes that may alter the drug's pharmacokinetics and pharmacodynamics.[10] On a related note, patients with comorbidity are found to have a 2 fold risk of experiencing ADR compared to patients with no known medical illnesses, possibly due to the complex interactions between multiple drugs and disease states. Several studies have identified the female gender as one of the potential risk factors for experiencing ADR. Our study reported a 1.5 fold risk in females to experience ADR than males, which corresponds to current literature.[9,11,12]

CONCLUSION

Although living in a time of global emergency and seeking effective treatment, drug safety must never be ignored, especially when it comes to drug interactions. In patients with COVID-19, anticoagulant therapy was suggested as a mitigating strategy. However, there has been limited research on the adverse effects of anticoagulants in patients with COVID-19. Unfractionated heparin was the most common anticoagulant associated with ADRs. Due to the wide range of biological activities of heparin, all of its adverse effects are related to them, Bleeding is the most critical safety concern that directly results from its effectiveness as an anticoagulant. Thrombocytopenia is the most severe non-bleeding adverse reaction caused by heparin. A common and unavoidable side effect of heparin is the development of skin lesions due to delayed-type hypersensitivity reactions.

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