ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 9| Issue: 5| May 2023|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2023: 8.224 || ISI Value: 1.188

SIDE EFFECTS TO ANTITHROMBOTIC THERAPY IN PATIENTS WITH COVID-19: POSSIBLE NEGATIVE IMPLICATIONS AND UNDERSTUDIED FACTORS

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ABSTRACT

Objective: *To bring forth possible negative implications and side effects to antithrombotic therapy in patients with COVID-19 infection.*

Materials and Methods*: This review was done based on existing data and utilizing resources such as books, journals and online publications using search engines.*

Results: *The study took into account results from large studies. Inferences from ACTIV-4a, REMAP-CAP, ATTACC studies as well as ACTION, INPIRATION and RAPID were considered. Contrasting findings and understudied areas were also highlighted in the study.*

Conclusions: *There is a need for continuous and judicious monitoring of patients on DOACs. It was revealed that there can be changes in plasma drug concentrations owing to complex drug interactions with metabolic pathways and dysregulations induced by the disease itself. The bleeding risk was one of the main concerns. Routine thromboprophylaxis should be under question. Bleeding risk had relation to whether therapeutic, subtherapeutic or prophylactic therapy was used. There are some contrasting findings across studies which needs to be clarified by further studies.*

KEYWORDS: *Antithrombotic therapy, SARS-COV-2 infection, DOACs*

INTRODUCTION

Severe Acute Respiratory Syndrome Corona Virus-19, shortened as SARS-COV-2, caused by a member of the Corona-viridae family led to an outbreak of respiratory infections which started off from Wuhan, China. It spread across countries and continents in a very rapid manner and was declared as a Pandemic by the World Health Organization on 11th of March, 2020. Ever since then, the treatment and vaccination for prophylaxis were some of the most sought-after medical answers for a long time. *The purpose* of this research is to study side effects to antithrombotic therapy in patients with SARS-COV-2 infection. *The aim* of this study is to shine light onto the possible negative side of therapy in patients with SARS-COV-2 infection using existing literature and clinical study findings. The main *objectives* are to clarify possible negative implications and understudied factors in treatment with antithrombotic therapy in patients with SARS-COV-2 infection.

MATERIALS AND METHODS

The given research was carried out on the basis of existing data, collected from journals, books and online publications. An example of this would be a Report published in Italy. This Report took into account Direct-acting Oral Anticoagulants (DOAC) in patients with SARS-COV-2 infection. The report analyzed 1039 patients hospitalized SARS-COV-2 pneumonia and candidates for antiviral therapy, of whom 32 were on treatment with a DOAC [9]. 12 patients received concomitant therapy with DOAC during antiviral treatment. Each patient was subjected to a C-trough DOAC level comparison using the one measured at a thrombosis center preceding the hospitalization. In the patients who received concomitant therapy, a significant increase in DOAC plasma levels was seen after hospitalization. This can be explained by the following mechanism: DOACs interact with P-glycoprotein and/or cytochrome P450 (CYP)-based metabolic pathways. Antiviral drugs, such as Remdesivir are substrates of CYP 3A4, CYP 2D6, and CYP 2C8. Dexamethasone is also an inducer of CYP3A4. To further complicate the picture, SARS-COV-2 infection also has an effect on CYP regulation. The multiple drug-drug interactions (antiviral, antibiotics, antihypertensive, bronchodilators, and immunosuppressive drugs), in addition to metabolic alterations that are induced by the acute disease, can cause an unpredictable and unstable DOAC anticoagulant effect, exposing patients to the risk of uncontrolled bleeding or thrombotic complications [9]. DOAC was also the focus of interest in another nationwide cohort study using the Swedish Register [10]. In this study including more than 100 000 DOAC users, the ongoing use of these class of drugs was not associated with a decreased risk of hospital admission for laboratory-confirmed SARS-COV-2 infection nor for the composite of ICU admission or death due to laboratory-confirmed COVID-19. The findings were consistent in analyses with two different comparator groups, as well as across DOAC subtypes.

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RESULTS

Therapeutic options, regimens and measures were revised and re-revised over time for the betterment of patients and clinical outcomes. SARS-COV-2 infection has been associated with inflammation and a prothrombotic state, with increases in levels of fibrin, fibrin degradation products, fibrinogen, and D-dimer. It has been found that SARS-COV-2 infection induces a complex inflammatory response that includes initiating the coagulation cascade related to von Willebrand factor, factor VII release, factor V upregulation, and platelet activation [1,2]. Circulating biomarkers reflecting systemic inflammation and coagulation activation (e.g., d-dimer and C-reactive protein) are independently associated with a greater risk of respiratory failure, thrombosis and death in patients with Covid-19[3]. Although, respiratory compromise is the cardinal feature of the disease, early studies have suggested that elevated circulating D-dimer levels are associated with mortality [4,5]. Due to the state of hypercoagulability associated with SARS-COV-2 infection, use of antithrombotic therapy for preventing many of the thrombotic complications came to practice. However, the relative risk versus benefit of antithrombotic therapy have not been addressed with clear distinction as of till now. New findings and reports add more insight to the applications of antithrombotic drugs in this scenario day by day. More anticoagulant bleeds have occurred during the pandemic, and more patients have delayed seeking medical attention for Vitamin K antagonists (VKA) - associated bleeding [6,7]. This however was due to the effect of the pandemic itself and the strict lockdown measures that came into practice which forced many of the outpatients who received anticoagulants for other reasons to lose control of their ideal coagulation profile. Even though this cannot be directly attributed to the side effects of antithrombotic therapy in patients with SARS-COV-2 infection, it was also a major factor that led to antithrombotic therapy being discussed and bleeding risk studied during the pandemic. The most important entities associated with a negative effect of anti-thrombotic therapy in patients with SARS-COV-2 infection that needed to be addressed were bleeding and possible drug interactions with other medications for SARS-COV-2 infection. Another important issue to mention is that even after adequate thromboprophylaxis; symptomatic venous thromboembolism (VTE) occurs in 4.4% of patients, ischemic stroke in 2.5%, and myocardial infarction in 1.1% [8]. Oftentimes the mechanisms underlying the effects of these entities are complex and they may be interspersed as well.

DISCUSSIONS

The major negative effect that is tailed along antithrombotic therapy is bleeding. The use of anticoagulants was associated with an increased risk of bleeding and bleeding related complications in patients with SARS-COV-2 infection. One of the studies to point out this was a single center retrospective analysis of 355 adult patients with confirmed diagnosis of SARS-COV-2 infection from March 1 to May 31, 2020 [11]. It analyzed the relationship between degree of anticoagulant dose and bleeding events by site. The bleeding rates were subjected to comparison among the therapeutic, subtherapeutic and prophylactic dose categories of anticoagulants. The former two categories of dosing were given based on a background of elevated D-dimer levels. Hence the severity of the infection was respected in this manner. The findings from the study revealed a higher bleeding risk which was proved by the incidence of more major bleeding events in the therapeutic dose category. The subtherapeutic groups had lower incidence of bleeding events. The above findings establish the fact that anticoagulants and thereby the practice of antithrombotic therapy itself carries a risk for increased bleeding episodes. The additional fact that could be understood from the findings above is the relationship between the bleeding risk and the dosage of the formulations used. The dosage categories; that is whether prophylactic, subtherapeutic or therapeutic dosages had an impact on the bleeding events. Another study evaluated Association of Treatment Dose Anticoagulation with In-Hospital Survival [12]. The risk of bleeding was also compared in the same study. 786 (28%) of the 2,773 patients with SARS-COV-2 infection hospitalized in the study got systemic treatment-dose anticoagulants during their hospital stay. When anticoagulants were used to treat patients, the in-hospital mortality was 22.5% with a median survival of 21 days as opposed to 22.8% and 14 days for patients who did not get treatment-dose AC (anticoagulants). But when comparing those who received prophylactic dosage AC or did not receive AC to those who got treatment-dose AC, the latter had a higher probability of needing invasive mechanical ventilation. The study also probed into the connection between bleeding events and systemic treatment-dose AC delivery. A diagnosis code for major bleeding was kept which included events from intracranial hemorrhage, hematemesis and hematuria to anal hemorrhage. The code was reinforced by strict measurable variables like Hemoglobin values and presence of transfusions to signify the severity. In patients not receiving therapeutic AC, 1.9% had bleeding events compared with 3% in patients receiving therapeutic AC. Among this 3% patients on therapeutic AC who had bleeding, 63% had the bleeding event after AC initiation and only 37% had a bleeding event before AC initiation. This aids us to analyze the link of bleeding events and their attributability to ACs in general. Also, in the same study bleeding occurred more frequently in intubated patients (30 of 395; 7.5%) than in non-intubated patients (32 of 2378; 1.35%). However therapeutic dose categories having a higher incidence of organ support or mechanical ventilation was a fact that further needed attention. Throughout literature opposing findings were found on outcomes and requiring organ support or ventilation, but the differences mainly were skewed based on the severity; that is whether the patient was non critically or critically ill. Both critically ill and noncritically ill patients with SARS-COV-2 infection have been the target of finished randomized clinical studies of antithrombotic medications. When compared to regular prophylactic heparin, therapeutic-dose anticoagulation with heparin did not enhance clinical outcomes and was linked to an increased risk of severe bleeding events in critically ill patients. SARS-COV-2 infection trials in patients who are only moderately unwell have produced conflicting findings. When compared to usual-care thromboprophylaxis, therapeutic-dose heparin or low-molecular-weight heparin increased the

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likelihood of survival until hospital discharge with a decreased need for organ support in the international, adaptive, multiplatform randomized clinical trial [13] that combined data from the ACTIV-4a, REMAP-CAP, and ATTACC studies. In contrast, there was no difference in the primary result between the therapeutic-dose and prophylactic-dose groups in the ACTION [14] INPIRATION [15] and RAPID [16] studies.

CONCLUSIONS

SARS-COV-2 infection itself is associated with proinflammatory and a prothrombotic state. Usage of DOACs in patients needs to be cautiously monitored as antiviral drugs such as Remdesivir, corticosteroids and SARS-COV-2 infection itself can interact with metabolic pathways and hepatic enzyme systems thereby altering the serum levels of DOACs. The altered drug pharmacokinetics may lead to an increase in bleeding risk predisposing the patient to bleeding events. In contrast to this drug interactions which activate hepatic enzyme systems may lead to faster clearance of DOACs from circulation thereby removing them from the spectrum of adequate antithrombotic protection leading to thrombosis. Another important factor that needed to be considered is the dosage regimen whether: therapeutic, subtherapeutic or prophylactic dosage used. The cohort study example described in the study pointed out that bleeding risk was higher when comparing treatment dose AC with non-treatment dose AC. Even though survivability on invasive mechanical ventilation was longer in patients using treatment dose AC, higher incidence of patients requiring mechanical ventilation was also in the same group. Organ support and invasive mechanical ventilation was being more associated to the treatment dose AC group is another factor that must be taken into consideration. In addition, prophylactic heparin and therapeutic-dose anticoagulation with heparin did not enhance clinical outcomes and was linked to an increased risk of severe bleeding events in critically ill patients. However conflicting findings have found regarding outcomes, requiring organ support or ventilation in other studies. This could be related to whether the patient is critical or non-critical. Conflicting findings mostly arose when the subjects of study were moderately unwell patients. Increased survival was inferred from ACTIV-4a, REMAP-CAP, and ATTACC studies, whereas therapeutic-dose and prophylactic-dose groups in the ACTION, INPIRATION and RAPID studies did not find significant differences. This also bring forward need for larger studies with methods to remove bias and better standardization. Along with this therapeutic drug monitoring, better analysis of drug interactions in patients with SARS-COV-2 infection and bleeding risk stratification systems need to be considered.

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