

Should we avoid heparin based anticoagulants in “COVID-19 infection-vaccination related thrombosis”? Insights from the HIT like syndrome observed with infected cases.

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Systematic Review

Keywords: Heparin induced thrombocytopenia, Anti-platelet factor 4 antibodies, ChAdOx vaccine

Posted Date: April 5th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-393180/v1>

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Abstract

Background: Recent reports of the prothrombotic states announced in the recipients of the ChAdOx vaccine, similar to HIT sounded alarm bells internationally.

The sole outcome parameter of this systematic review was to detect similar cases of Prothrombotic state in COVID-19 infected patients

Methodology: *Embase, Medline and the Cochrane Central Register* were used to search for specific keywords such as “COVID-19” OR “SARS-CoV-2” AND “Heparin induced thrombocytopenia” for relevant publications up to 1st of April 2021. The systematic review was performed using PRISMA protocol.

Results: Nine cases reports/series have been identified including 18 cases, venous thrombosis was the commonest type of observed thrombosis accounting for 72 % of cases, the mean age of cases was 57±4.

Conclusion: Similar episodes of HIT were detailed in several case reports of COVID patients. This suggests a common pathogenesis and warrants a screening of all COVID-19 patients presenting with thrombo-embolism using anti-PF4 antibodies and using non heparin based anticoagulants for their management.

Background

Currently, over 150 coronavirus vaccines are under development. In an attempt to stop the ongoing pandemic, numerous countries have issued emergency use authorization for many of those vaccines. (1) This hectic vaccine rollout means that not enough is known about their short and long-term consequences. In March of this year, reports broke out of strokes and prothrombotic states in ChAdOx vaccine recipients. The use of this vaccine was subsequently suspended in several European countries. (2)

The European Medicines Agency (EMA) stated concern for the safety of the ChAdOx vaccine. However, Greinacher and colleagues showed (in a preprint) the serologic profile of patients who developed this unusual set of symptoms after the ChAdOx vaccine. They concluded that the prothrombotic state in these patients is similar to Heparin-induced thrombocytopenia (HIT). All nine patients showed positive anti-platelet factor 4 antibodies (anti-PF4), frequently seen in heparin recipients. None of these patients were on heparin before getting vaccinated. This implies that the ChAdOx vaccine can potentially induce such autoantibodies.(3)

The sole outcome parameter of this study was to review similar cases of Prothrombotic state associated with COVID-19 infection not vaccination.

Methodology

Embase, Medline and the Cochrane Central Register were used to search for specific keywords such as "COVID-19" OR "SARS-CoV-2" AND "Heparin induced thrombocytopenia" for relevant publications up to 1st of April 2021. The systematic review was performed using PRISMA protocol.

Study Selection criteria Population:

No specific age group or sex

Intervention: COVID-19

Comparison: No comparison has been a purpose of the study

Outcome: Heparin induced thrombocytopenia

Observational epidemiological studies and case reports addressing inclusion criteria were included

Results

Several reports of HIT were reported (a total of 9 reports/series including 18 cases) before the current vaccine rollout; these were reviewed and summarized in table 1(4–12). All the reports incriminated heparin in the development of the observed prothrombotic state. These patients received heparin due to one of three reasons:

-Initial presentation with thrombosis

-Increased risk of thrombo-embolism development due to an underlying medical condition e.g. atrial fibrillation

-Extra membrane corporeal oxygenation

Discussion

+Is this an old, misinterpreted feature of Coronaviridae or is it a brand new feature?

A rise in similar reports following ChAdOx vaccination indicates that heparin might not be the cause of this HIT-like syndrome after all. Instead, SARS-CoV-2 could induce an autoantibody profile similar to that of HIT.

Also the pattern of observed thrombotic events is mainly venous, thus mimicking that observed in recipients of ChAdOx vaccination.

+Diagnostic and therapeutic implications:

These findings necessitate an update to laboratory testing and treatment of COVID-19 patients presenting with thrombosis, through the following:

-Routine anti-PF4 testing.

The high prevalence of anti-PF4 in COVID-19 patients previously diagnosed with HIT (as mentioned in table 1) warrants screening of this antibody profile in COVID-19 infected patients presenting with thrombotic events as well as in recipients of ChAdOx vaccination.

-Alternative anti-coagulants.

Currently, three non-heparin anticoagulants, namely Danaproid, Lepirudin, and Argatroban, are used in HIT as alternative anticoagulants; this is because they do not cross-react with HIT antibodies. Low molecular weight heparin (LMWH) similarly is not to be used in COVID-19 patients and ChAdOx vaccinated individuals because of its cross-reactivity with PF4 autoantibodies. Warfarin, besides, is discouraged in HIT due to a paradoxical increase in the thrombotic tendency.

High-dose intravenous immunoglobulins are one of the most important and established therapies for HIT.

A final therapeutic approach of importance is using Hep-like molecules to disrupt the PF4–GAG complexes. This has been considered in the treatment of HIT and could be used as a treatment for the prothrombotic state in COVID-19 patients and ChAdOx -vaccinated individuals.(13)

Figure 1 outlines the diagnostic and therapeutic implications suggested above

Conclusion

Increasing evidence suggests that SARS-CoV-2 is an independent risk factor in the development of PF4 autoantibodies regardless of prior heparin therapy. The reports encountered after ChAdOx vaccination and earlier reports after infection provide strong evidence for such a hypothesis. This information warrants clinicians to screen such autoantibodies in any COVID-19 patient and ChAdOx vaccinated individuals presenting with a thrombotic event. It may also lead to changes in the anti-coagulant regimens used for such patients and the use of new treatments such as immunoglobulins and Hep-like molecules that can disrupt PF4–GAG complexes. In view of the available data, avoidance of heparin-based anticoagulants in COVID-19 patients and vaccinated individuals should be warranted. It also remains unclear, why such Prothrombotic state has been observed solely with COVID-19 infection, and with ChAdOx vaccine and not with the other available vaccines. This mandates a close follow up of recipients of other available COVID-19 vaccines to detect if similar Prothrombotic events would develop or not.

Declarations

Conflict of interest:

None

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Tables

Table 1: Summary of COVID-19 related cases of Heparin induced thrombocytopenia

Authors	Country	Age	Type of prothrombotic state
Madala et al (4)	USA	65	Lacunar infarct in basal ganglia and right sided hemiplegia
Kewan et al (5)	USA	56	DVT
Lingamaneni et al (6)	USA	63	DVT
Sartori et al (7)	Italy	78	DVT
Bidar et al (8)	France	62	Pulmonary embolism
		38	Deteriorating oxygenation
Ogawa et al (9)	Japan	37	DVT, massive pulmonary thromboembolism
Daviet et al (10)	France	46	DVT
		50	Intracardiac thrombosis
		43	DVT
		63	Stroke
		59	DVT
		57	None
Phan et al (12)	China	43	DVT/Pulmonary micro-thrombi, deteriorating oxygenation
		69	
Lozano and Franco (11)	Spain	45	None
		71	
		90	
Summary		Total of 18 cases	13 presented with thrombotic events (72%) DVT/pulmonary embolism: commonest prothrombotic event (9 cases/61%)

Figures

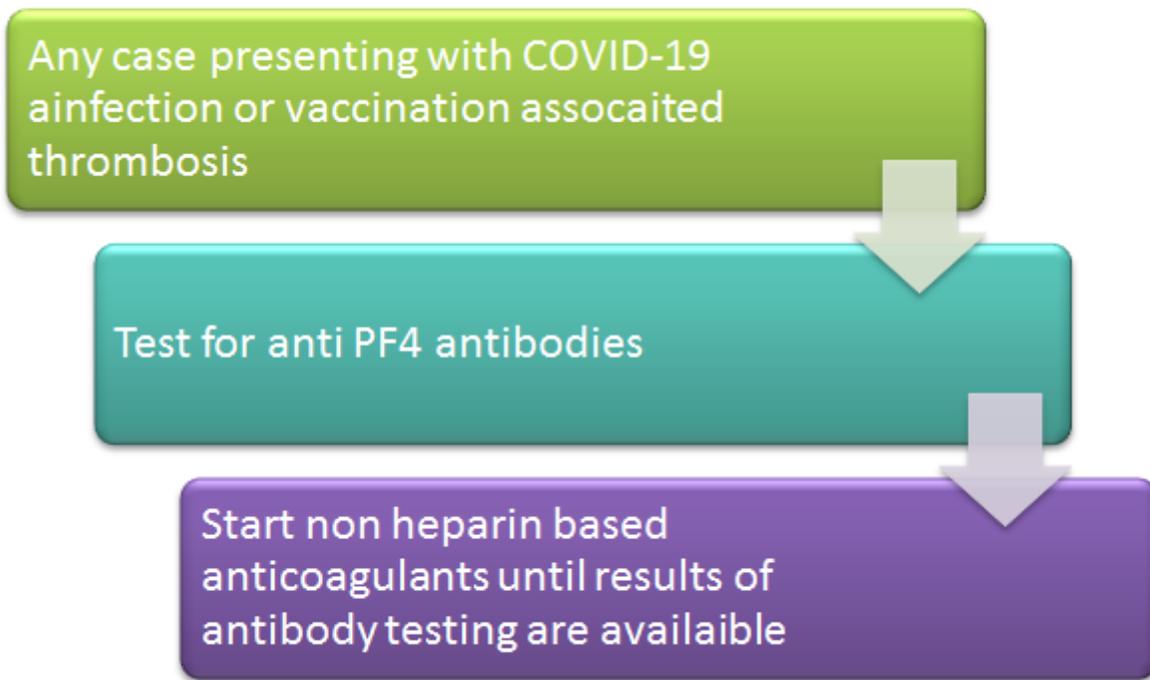


Figure 1

Title: Suggested management of Prothrombotic event associated with COVID-19 infection or vaccination

Abbreviations: PF4: Platelet Factor 4