Incidence of Heparin Induced Thrombocytopenia in ECMO patients: A cross-sectional Study

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Abstract

Purpose: Patients under the support of Extra Corporeal Membrane Oxygenation (ECMO) are more susceptible to thrombocytopenia. There are several causes for this thrombocytopenia. A major causative is Unfractionated Heparin (UFH) provided to prevent thrombosis during ECMO operation. However, the accurate incidence of Heparin Induced Thrombocytopenia (HIT) on patients under ECMO remains largely unknown. The goal of this study is to determine of incidene of Heparin Induced Thrombocytopenia in patients receiving both the types of Extra Corporeal Membrane Oxygenation.

Methods: This cross-sectional study included 70 patients in both VA-ECMO and VV-ECMO from two large hospitals in the Netherlands, Germany or Belgium with more patients on ECMO in ICU. Selected patients were hospitalized more than 3 days with thrombocytopenia and their platelet counts were recorded at different time interval. To confirm HIT tests such as 4T score and ID-H/PF4 PaGIA were performed to determine anti-PF4/Heparin particles.

Discussion: This study estimates the incidence of HIT in patients on VA- and VV- ECMO. This may lead to the use of other anticoagulants during ECMO.

Background Information

Rationale and Justification of the Study:

There are a lot of patients for whom ECMO serves as a treatment or bridge to transplant. All these ECMO patients are treated with Unfractionated Heparin at regular intervals to avoid thrombosis that occurs in ECMO machine during operation. Continuous injection of heparin to the human body causes several complications including bleeding, bruising, thrombocytopenia and many more. Of all the complications due to heparin on ECMO patients, Heparin-induced Thrombocytopenia is the most common and serious. This study aims to identify the incidence of thrombocytopenia in ECMO patients and stress the need for alternative anticoagulants.

Heparin-induced thrombocytopenia is a life-threatening disorder that occurs due to exposure to unfractionated or (less commonly) low-molecular-weight heparin. Classic symptoms usually include a low platelet count (<150,000 per cubic millimeter) or a relative decrease ranging from 30 percent less than the baseline in some patients to a relative decrease of 50 percent or more in most patients. Among these patients, thrombotic complications develop in approximately 20 to 50 percent of them. HIT is caused by antibodies against complexes of platelet factor 4 (PF4) and heparin. These antibodies are present in nearly all patients who receive a clinical diagnosis of the disorder [1]. When compared to other drug-induced thrombocytopenias, HIT does not usually

cause bleeding, but instead causes thrombosis.

Extra Corporeal Membrane Oxygenation can deliver purely respiratory support (VV-ECMO) and specifically respiratory support with right ventricular support (VA-ECMO). Today, with careful patient selection, VV-ECMO is used as a rescue therapy to allow for recovery or bridge to transplant for hypoxic respiratory failure while the latter is used as recovery for severe refractory cardiogenic shock [2]. The thrombotic complications that may occur when blood is exposed to artificial surfaces within the ECMO circuit can be mitigated using systemic anti-coagulation. Unfractionated heparin is the most common anticoagulant used to prevent the formation of thrombus within the ECMO circuit [3]. This UFH induces thrombocytopenia in ECMO patients (HIT). Therefore, the objective of this study is to determine the incidence of HIT in patients undergoing both the types of ECMO.

Related Studies:

There were no much studies conducted or reported on the incidence of heparin induced thrombocytopenia in ECMO patients. However, there was one study [4] which managed to determine the prevalence of HIT in VA-ECMO patients especially those who suffered from cardiogenic shock and also 90 day mortality rate in those patients. It was a retrospective nationwide study with patients from 20 French centers between 2012 and 2016. Selected patients were hospitalized for more than 3 days with high clinical suspicion of HIT and positive antiPF4/heparin antibodies. Patients were classified according to results of functional tests as having either Confirmed or Excluded HIT. Out of 5797 patients only 39 patients met their inclusion criteria with HIT confirmed in 21 patients.The results show that drug-induced thrombocytopenia tend to be more frequent in Excluded HIT at the time of HIT suspicion. The platelet course was similar between Confirmed and Excluded HIT. Mortality rate was 33.3% in Confirmed and 50% in Excluded HIT.

There was another study which determined the frequency of HIT in patients treated with UFH and low molecular weight heparin (LMWH) as prophylaxis after hip surgery [5]. It was a randomized, double-blinded clinical trial with 665 patients. They confirmed HIT with the decrease in platelet count after 5 days of heparin treatment. They also conducted these test in a subgroup of 387 patients with regardless to the platelet count. The result showed that HIT occurred in 9 of 332 patients who received unfractionated heparin and in none of 333 patients who received low-molecular-weight heparin. In the subgroup of 387 patients, the frequency of heparin-dependent IgG antibodies was higher among patients who received unfractionated heparin.

Relevance of the study:

As stated in the background information, HIT causes thrombosis in patients. Thrombosis in HIT can lead to limb gangrene leading to amputation of the leg or even death in some cases [6]. Thrombosis in HIT is associated with a mortality of approximately 20–30% of the patients. Female are susceptible to thrombotic stroke as an outcome of their HIT [7]. According to Salter BS et al. [8], strong risk factors for HIT include:

- the duration of heparin therapy ($>$ 3 days)
- the type (UFH $>$ LMWH $>$ fondaparinux) and dosage of heparin
- the patient's sex (female $>$ male)

The use of UFH in patients on ECMO to prevent thrombosis increases the risk of thrombocytopenia. This leads to several complications in critically ill ECMO patients. For instance, a patient was pre-operatively exposed to both unfractionated and low-molecular-weight heparin as she underwent five hemodialysis sessions. HIT

caused right common and external iliac vein and renal graft artery thrombosis, resulting in graft loss. This may also happen in patients under ECMO as they are exposed to UFH too. This study would lead to changes in the anti-coagulants used during ECMO operation. This will also be used to determine the various causes of thrombocytopenia other than heparin.

Research Question

What is the incidence of thrombocytopenia in VA-ECMO and VV-ECMO patients due to Unfractionated Heparin?

Research Objective

The goal of this study is to determine of incidence of Heparin Induced Thrombocytopenia in patients receiving both the types of Extra Corporeal Membrane Oxygenation.

Outcomes

Primary Outcome:
Incidence of HIT in VA-ECMO and VV-ECMO
Secondary Outcomes:
Other causes for thrombocytopenia, time-course of platelet count, other complications due to HIT

Hypothesis

The need for this study is to prevent the use of UFH on ECMO patients if the incidence of HIT is higher. The patients on VA- and VV- ECMO receive the same amount of UFH. So, the hypothesis is formulated as:
Patients receiving Extra Corporeal Membrane Oxygenation and Unfractionated Heparin are at high risk of Heparin Induced Thrombocytopenia.
Null Hypothesis:
Incidence of HIT is the same in patients on VA-ECMO and VV-ECMO
Alternate Hypothesis:
Patients on VA-ECMO develop HIT more likely than patients on VV-ECMO.

Methods

Inclusion Criteria:
The incidence of HIT has been reported in ECMO patients who are under UFH for a minimum of 3 days. So, adult patients in ICU admitted under VA-ECMO for atleast 3 days and patients under VV-ECMO for atleast 3 days are included for this study. This is done to make sure the incidence of HIT in both Veno-venous and Veno-arterial ECMO. This study will be conducted in two hospitals which have large number of ECMO patients in the ICU within Germany, Netherlands or Belgium. The study of platelet count will be carried out in the

laboratory of the same hospital. Either the patients or their family member will be provided with written informed consent before the start of the study. This study will take place until the minimum sample size is satisfied.

Exclusion Criteria:

The obstetric patients will not be included in the study even though they are more prone to thrombocytopenia [7]. This is because it is less likely that pregnant women are under ECMO. Children are also excluded from the study as there is a separate ECMO support for children. It is also due to the huge variation that may appear in the patient characteristics. Patients who have pre-clinical history on HIT will also not be included.

Data Collection:

The measurement parameters used for this study are platelet count, timing of onset. Firstly, an automated analyzer will be used to measure the platelet counts in the patients. The platelet counts will be calculated at different time intervals such as at admission, at HIT suspicion, at day 5 after suspicion and at day 7 after suspicionBased on the platelet count, 4Ts score will be provided. If the 4Ts score is high, ID-H/PF4 PaGIA will be performed. The reliability and validity of this test has already been studied and validated [9].

Procedure

Study Design:

In this study, the patients on VA-ECMO and VV-ECMO will be divided into two groups and administered with UFH to prevent thrombosis during ECMO. These patients will be continuously tested for platelet count by means of standard automated analyser. Automated analyzer is an instrument designed to perform clinical trials in several blood samples in a short period of time with minimal human assistance. If the platelet count is $50–70\times10^9$/L, 4Ts score will be provided. The 4Ts Score is a clinical scoring system to differentiate patients with HIT from those with other causes of thrombocytopenia. The 4Ts in the 4T score are Thrombocytopenia (platelet count), Timing, Thrombosis and Other causes of Thrombocytopenia are not evident. Each 'T' will be given scores from 0 to 2. Therefore, the maximum score will be 8 [10]. The risk of HIT based on 4Ts score is given in table 1.

4T score	Risk
0-3	Low
4-5	Intermediate
6-8	High

Table 1: Risk of HIT based on 4T score [10]

If the score is low, the patient can be declared free from HIT. They do not require any further testing. If the scoring is high, the patient's blood sample will be sent for ID-H/PF4 PaGIA, the best particle gel immunoassay to rule out HIT.

Potential Risks and Burden:

There will be no risks or burden to the patient associated with the clinical trial as this is a very minor part of their entire ECMO support. They will already be used to clinical tests and treatments. There will be no side effects due to this trial because it is a study to determine incidence and not provide treatment. The burden

lies in the hands of the clinician, who needs to recommend another anticoagulant even if they are suspected to have HIT. But this will be outweighed by the ill effects due to heparin if the patient has HIT.

Sample Size:

The assumptions has been made such that the ID-H/PF4 PaGIA rules out HIT to the maximum. For the Confidence Interval of 95%, the sample size was estimated to be 70 patients per group with effect size of 0.5, significance level of 5%, power of 80% and drop out rate of 11%. Therefore, a total of 140 patients will be included in this study.

Statistical Analyses:

The continuous variables of patient characteristics and other continuous variables such as platelet antibody levels will be expressed in medians of interquartile range. The variables with normal distribution will be assessed using t-test and those with non-normal distribution will be assessed using Mann-Whitney test. The categorical variables of patient characteristics and variables such as bleeding signs will be expressed in percentages and assessed using chi-square test. The platelet counts over time will be analysed using mixed-effect ANCOVA (Analysis of Covariance) with the ranks of platelet counts at regular intervals. This is due to the varying platelet counts.

All the statistical analysis will be performed using SPSS software.

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