Reviewer’s report

Title: Monitoring of argatroban and lepirudin anticoagulation in critically ill patients by conventional laboratory parameters and rotational thromboelastometry - a prospectively controlled randomized double-blind clinical trial

Version: 0 Date: 01 Sep 2017

Reviewer: Lachlan Miles

Reviewer's report:

General comments

The overall argument of this small sub-study of a larger randomized controlled trial is that aPTT does not provide an effective estimate of relative lepirudin or argatroban level, despite being elevated in the presence of the drug in critically ill patients. In contrast, various ROTEM parameters provide a moderate correlation with drug effect, despite no change in maximum clot firmness. This is in keeping with our current understanding of coagulation, as these drugs should exert no effect on platelets or fibrinogen. This is an interesting finding, as the development of new theories of anticoagulation (Hoffman, Blood Rev, 2003) suggests that aPTT and PT are limited in the presence of multiple confounding factors.

There is no reporting of the process used for randomization or blinding. Whilst I appreciate that this has been reported as part of the aforementioned parent study, it is still not acceptable for a reader to search for information regarding these processes, especially when there are substantial trends towards patients in the argobatan group being older and heavier.

The study is substantially limited by its small sample size. The substantial delay in publishing these data also means that one of the drugs tested (lepirudin) has been withdrawn from the market. The study is also limited by an absence of reporting of clinically significant outcome data. The study authors have made an oblique reference to loss of CVVH filters despite the increase in aPTT, but have not reported the incidence of this event, nor any other thrombotic complications. These events should at the very least be reported, as whilst poor correlation between aPTT and drug levels are of interest, some form of meaningful clinical outcome would increase the interest and generalisability of this paper.

From a statistical perspective, whilst an effort has been made to account for repeated measures using reduced p-values, a more statistically robust method, especially for the Bland-Altman plots used in figure 5 and 6 has been described previously by Myles and Cui (Myles, Br J Anae, 2007). Further statistical advice should be sought as to which of the techniques, those used by the authors here or those proposed by Myles and Cui, are more appropriate. I am not able to make this determination myself.
Overall, this manuscript presents an interesting thesis, but the study is severely limited by:

1. The small sample size of the study and lack of information on how it was determined;
2. The statistical methods used to correct for repeated measures;
3. The failure to report information regarding inclusion, randomisation and blinding for the parent study;
4. The failure to report clinically significant outcomes with respect to thrombotic complications.

Abstract

Page 5, line 14: The authors outline the taking of blood at various time intervals "after argatroban or lepirudin infusion". It is unclear to the reader if this refers to commencement or cessation.

Page 6, line 1: The authors state that they have shown "in critically ill patients, TT and ROTEM parameters provide better correlation to argatroban and lepirudin plasma concentrations than aPTT". The information presented in the abstract shows no evidence to justify this statement. Include additional information comparing aPTT to ROTEM/TT that justifies this statement or revise.

Background

Page 7, line 5: The authors outline the excretory pathways for both agents, and state that elimination is hepatic for argatroban and renal for lepirudin. This is followed by the sentence: "Thus both drugs have to be carefully titrated in patients with reduced kidney or liver function". This sentence is internally inconsistent with the prior statement (i.e. if lepirudin is completely renally excreted, why must hepatic function be taken into account?). Please clarify.

Page 7, line 7: The authors use the term "critically ill" when referring to a paper by Doepker et al. Please provide a less nebulous definition for "critically ill".

Page 7, line 18: The authors make reference to the Child-Pugh classification system when defining hepatic impairment, and in the subsequent sentence, state that many critically ill patients "do not meet the criteria of hepatic cirrhosis". Cirrhosis is a diagnosis made on imaging or histopathology, not the diagnostic criteria of Child-Pugh. Patients with acute hepatic failure may not have macroscopic or microscopic features of cirrhosis. Please remain internally consistent.
with these terms. A better phrasing would be "do not fulfil the Child-Pugh criteria for hepatic impairment".

Page 8, line 17: The authors assert that viscoelastic coagulation assays have "been proven beneficial as part of goal-directed bleeding management in patients with major haemorrhage". The article cited refers to cardiac surgery, and not major haemorrhage. Furthermore, it could be argued that this systematic review has been supplanted by more recent evidence questioning the role of VCAs in this scenario. A more cautious statement supported by more recent evidence as well as a more specific reference to the patient population in question is in order.

Page 8, line 19: The authors reference the roles of INTEM and EXTEM in the assessment of "intrinsic coagulation activation" and "extrinsic coagulation activation". It could be argued that on the basis of improved understanding of coagulation through the cell-mediated theory that terms such as "intrinsic" and "extrinsic" are outdated. At the very least, some reference to the historic "common pathway" should be included.

Page 8, line 23: For an English-language journal, the term "platelets" would be preferred to "thrombocytes".

Methods

Page 8, line 7: Despite the inclusion criteria for the ALicia study being published elsewhere, I would feel more comfortable as a reader if it could be included here so that I can review them for myself.

Page 10, line 12: The authors state that sample analysis occurred between February 2010 and November 2011. This manuscript has been submitted for peer review in August 2017. Is there an explanation for the extended delay?

Page 10, line 20: Some further exposition is required for why patients on CRRT received such a low dose of lepirudin. One would assume that the use of CRRT somewhat restores drug excretion. Why is this not the case for lepirudin (i.e. molecular charge, molecule size, etc.)?

Page 12, line 7: A company and location reference for SPSS is required.

Page 12, line 12: Please see general comments regarding statistical correction for repeated measures. I feel that further statistical input is required to confirm the approach used by the authors is the correct one.
Results

Page 13, line 9: Some reference to the therapeutic drug ranges of argatroban and lepirudin would be of use, especially as some clinicians will be unfamiliar with lepirudin now that it has been withdrawn from the market. At first glance, it is hardly surprising the argatroban group had a higher concentration as it was infused at a higher dose.

Page 14, line 8: The authors state that 25 of the 478 ROTEM measures were assessed as invalid. How was invalidity defined?

Page 16, line 11: The authors state that lepirudin is licenced for anticoagulation in HIT. Is this still the case even though it has been withdrawn from the market?

Conclusion

Page 20, line 3: The authors state that monitoring argatroban or lepirudin with aPTT is "not appropriate" due to the poor correlation with plasma levels. This is a strong statement in the absence of clinically significant outcome data. The rates of bleeding and thrombosis have not been presented, and even if they were, an observational trial is required (one arm aPTT monitoring, one arm TT or ROTEM monitoring) to prove this. Moderation of the statement is required.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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