Reviewer’s report

Title: Dissecting genetic factors affecting phenylephrine infusion rates during anesthesia: a genome-wide association study employing EHR data

Version: 0 Date: 22 Mar 2019

Reviewer: Henning Bay Nielsen

Reviewer’s report:

This paper Zhang et al is highly interesting as it aims to provide new knowledge into clinical practice on how to use vasopressors and importantly whether it is possible to predict their effect. Currently one may suspect that vasopressors are used in an approach that leads to over-treatment for some patients while others may be undertreated. Importantly, it is in principle unknown whether current clinical practice is beneficial for patient outcome and one hopes that harm from use of vasopressors is not provoked. So my enthusiasm for the paper is high. In short the paper addresses whether the response from phenylephrine treatment of anesthesia-induced reduction in blood pressure is associated to genetic polymorphism. Using a database with medical data obtained during anesthesia authors locate approx 5000 subjects who qualify for analysis following evaluation of inclusion and exclusion criteria. From machine learning approach the cohort is divided in three blood pressure response groups (resistant vs intermediate vs sensitive) depending on the effect of phenylephrine infusion. Genetic analysis finds that a variant of EDN2 differentiate resistant vs sensitive groups.

General comments

The paper is well-written, methods seem acceptable and conclusion justified by data. Introduction and discussion sections may be too long in length. In addition, several comments in results section should be moved to discussion section.

Specific comments

Abstract

Consider to add whether whole genomic analysis was applied or whether specific genetic polymorphisms were targeted.

What is GWAS?

Consider to add info on inclusion vs exclusion criteria

Please add number of patients included
Acid-basis - do you mean acid-base?

sentence ".....Suggesting vascular tone" at Line 58 is not a result. Consider to move to conclusion

At page 3 line 12 EDN2 is introduced - it may be an advantage to provide the reader with info on which genes were targeted earlier in abstrat. What about beta1 and beta2 and alpha1 polymorphisms?

Introduction

page 4 Line 22.

Sentence "There are no ....." may be little hard statement as several data point to genetic influence on hemodynamic responses (see initial papers by Snyder and Joyner from 2007 or 2008. Please also take a look on recent data by Rokamp et al. Recommended is paper by Gjesing et al. in PlusOne from 2009 and Jensen-MK in Scand J Clin Lab Invest from 2009).

Page 5 Line 19

Most often I think phenylephrine is used as bolus rather than continous infusion.

L31 sentence "Thus ...." seems like this is said earlier in text. Consider to change to ".... infusion rate is highly variable...."

Line 38 to end of end of section should be moved to methods.

Methods

Consider to add info on what is general practice for use of vasopressors in your institution.

What kind of surgery is targeted? Is surgery in general anesthesia both non-cardiac and cardiac? Is spinal mainly orthopedic surgery? Do you have data on blood loss?

How come only systolic pressure was used to target groups? Any particular reason for why diastolic or even better MAP is not taken into account?

What are the cut off values for low vs high SBP?

Page 12 L36 seems like a discussion rather than presentation of results?!

Paghe 13 line 21 ".......suggesting...." interpretation of data should be moved to discussion

Page 14 first para seems same
Consider to include explanation on machine learning technology

It may be an advantage to present only two groups. Those who are considered resistant and those who may be sensitive. Reason is that systolic pressure is not that different between resistant and intermediate.

How come infusion rate is not provided in relation to body weight? - it is usually normal practice in anesthetic journals.

In table 2 text for pressure is mean SBP - does this mean MAP or is it the average?

Discussion

too long in length. please limit text to the essential info.

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

Yes

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

Yes

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.

I recommend additional statistical review

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