PCRC Proposal Cover Sheet

Title:"Current practice variations in the treatment of intraoperative hypotension"

Linda Peelen PhD Epidemiologist Wietze Pasma DVM Data manager Arjen Slooter MD, PhD Neurologist-intensivist Jon Wanderer MD, MPhil Anesthesiologist Jesse Ehrenfeld, MD, MPH Anesthesiologist

Introduction

Recently, there is a growing interest in the relation between intraoperative hypotension (IOH) and the occurrence of various postoperative adverse events.¹⁻⁶ An increasing number of studies show an association between IOH and outcomes such as mortality, acute kidney injury and myocardial infarction. However, this does not mean that we now understand 'how low we can go'.⁷ For example, heterogeneity in IOH definitions, outcome definitions and study populations make it difficult to draw firm conclusions about the exact IOH threshold. Nonetheless, the observational nature of the data in these studies may be the biggest problem, as residual confounding may still be of great influence. The main cause of residual confounding may be the current behavior of anesthesia providers. As circulatory management is a vital part of anesthesia practice, current patients are frequently $-$ if not constantly $-$ being treated for low blood pressure by anesthesia providers. Consequently, the observational data on blood pressure only do not contain the answer to 'what blood pressure is too low'. It is thus of great importance that we improve our understanding of our current circulatory management.

The choice of an anesthesia provider to treat a low blood pressure is likely based on the depth and duration of IOH, and its expected cause – such as anesthetic overdose, vasodilation or hypovolemia. Since the exact cause of IOH is not always crystal clear and there are various treatment options available, it is conceivable that large variation exists in the treatment – or nontreatment – of IOH. The purpose of this study is to describe and visualize the practice patterns of blood pressure interventions as a response to a decrease in blood pressure during anesthesia and depending on patient and procedural characteristics. The practice patterns that emerge from this study may provide an indication of what blood pressure thresholds are considered to be clinically relevant by anesthesia providers. This insight may direct future research on the relation between IOH and postoperative adverse events. Eventually these results may contribute to optimization of IOH treatment for specific patients.

Methods

IRB statement

The Colorado Multiple Institutional Review Board has approved the study of de-identified patient data from the MPOG database.⁸ The Institutional Review Board (IRB) of the University Medical Center Utrecht (UMCU) has reviewed and approved participation of the UMCU in the MPOG study database (12-253C). The IRB of the UMCU will be asked for a waiver for informed consent for this study protocol as cases will not be subjected to investigational actions. Patient confidentiality was guaranteed according to the Dutch law on personal data protection.

Study type

We propose a multicenter retrospective cohort study using de-identified case data from the MPOG database.

Patient inclusion criteria

All adult patients (aged \geq 18 years) who underwent elective, non-cardiac surgery with general anesthesia at one of the centers that participate in MPOG during a six year period (2010-2015) are included in the analysis.

Patient exclusion criteria

The following cases will be excluded from data collection and analysis:

- o Emergency or cardiac surgery
- o Patients who did not receive general anesthesia (the period of general anesthesia will be defined as the time frame with monitoring of $ECO₂$ and a continuous administration of inhalational anesthesia or TIVA)
- \circ Procedures with a surgical time less than fifteen minutes (time between surgical incision (Case Time "Procedure_Start_DT" , see Table 4) and dressing (Case Time "Procedure_End_DT")).

Data source

Data will be acquired from the MPOG database. A detailed general case information, preoperative history and data from the electronic anesthesia information management system (AIMS) will be obtained for each included case. General case information includes sex and age. Preoperative history consists of data elements with regard to cardiovascular comorbidity and ASA physical status. Electronic intraoperative anesthesia data consists of type and duration of surgery, hemodynamic variables, intraoperative fluids and medication. As different hospitals use different AIMS and warning systems with alarm setups, a certain clustering of data per hospital is expected. MPOG coordinators of participating centers will be asked for information about the artifact filters, protocols, warning systems, alarm setup or other interventions with regard to regulation of blood pressure treatments in their hospitals.

Determinant

The goal of this study is to find a blood pressure threshold that is most closely related to the onset of blood pressure treatment. Two types of thresholds will be analyzed for both systolic blood pressure (SBP) and mean blood pressure (MBP): an absolute threshold and a relative threshold. An absolute threshold is defined as the absolute blood pressure value as a threshold for IOH, whereas the relative threshold is defined as the percentile decrease from the preinduction blood pressure. This thus results in four different types of IOH thresholds. The subsequent descriptions and definitions of IOH and IOH thresholds apply to all four threshold types unless otherwise specified.

For each possible threshold value the start and end of all hypotensive episodes are identified. For SBP, values between 0 and 150 mmHg with 1 mmHg increments will be considered as possible absolute thresholds, whereas values between 0 and 110 mmHg with 1 mmHg increments will be considered to be possible MBP absolute thresholds. The relative thresholds for both SBP and MBP will range from 0 and 100% with 1% increments.

A hypotensive episode is defined as the time between the first blood pressure measurement below a given IOH threshold $(t = 0)$ and the first of two consecutive blood pressure measurements above the given threshold (Figure 1). A subsequent hypotensive episode only starts when the blood pressure drops below the particular threshold again, after a washout period of blood pressure above the threshold. Six minutes above the threshold or two consecutive measurements above the threshold – whichever comes first – are considered as the washout period. How multiple episodes are handled in relation to the onset of blood pressure treatment is discussed in the sections 'Effect modifiers'.

Invasive and non-invasive measurements

In the MPOG database, both invasive arterial blood pressure measurements (ABP) and noninvasive blood pressure measurements (NIBP) will be available. Two assumptions with regard to the availability of ABP and NIBP measurements will be made:

- \circ In case of only NIBP measurements, the estimated average interval between two measurements will be 3-5 minutes.
- o When both ABP and NIBP measurements are available, decisions with regard to blood pressure treatments are based on ABP measurements.

The validity of these assumptions will be verified by comparing the response time between cases with primarily ABP measurements and cases with primarily NIBP measurements (see paragraph 'Primary outcome'). When the mean onset of the first blood pressure intervention after the first hypotensive measurements differs more than six minutes (one minute more than the expected NIBP interval) between cases with ABP measurements and cases with NIBP measurements, the dataset will be split and we will stratify the entire analysis for ABP and NIBP measurements. If the difference is six minutes or smaller, cases with primarily ABP or primarily NIBP measurements will be pooled, and the use of ABP and NIBP will be used as an effect modifier. Additionally, blood pressure values between NIBP measurements will not be interpolated.

Blood pressure artifact filtering

In this study we are investigating the responses of anesthesia providers when confronted with a blood pressure value that is at that moment being displayed on the patient's monitor. Therefore, we refrain from using complex, time-dependent, artifact filters and will apply relatively simple artifact filtering as would be available in clinical practice.

The following artifact filters will be used:

- o Marked as artifact by the source system
- o Systolic >200 AND pulse pressure <50
- o Systolic > 150 AND pulse pressure < 30
- o Systolic > 100 AND pulse pressure <20
- \circ Systolic <= 0 OR Diastolic <= 0

Primary outcome

The purpose of the study is to relate the depth of IOH to the subsequent treatment of blood pressure by anesthesia providers. The primary outcome is therefore defined as the first blood pressure intervention that is applied with an IOH episode. The various blood pressure interventions are described in Table 1. The following secondary outcome measures will be considered:

- o All blood pressure interventions within an IOH episode.
- o Specific blood pressure interventions (according to Table 1)

Outcome data collection will consist of recording all blood pressure interventions that are applied within an episode of IOH (Table 1). The documentation of the timing of an administered intervention will not be exact. Within the AIMS registration it may therefore sometimes seem that the intervention was administered just before a drop in blood pressure. Therefore, all interventions are considered to be related to an IOH episode when they occurred between 5 minutes before the start of the IOH episode and the end of the episode.

Although intraoperative fluid administration will be recorded, the resolution in the electronic patient record for the actual timing of fluid boluses is expected to be insufficiently accurate to relate their timing to IOH. Therefore, only the sum of intraoperative fluid (crystalloids, colloids, blood products) will be described.

Table 1 - Intervention options with regard to intraoperative hypotension

Effect modifiers

The blood pressure threshold at which anesthesia providers will treat IOH is unlikely to be 'one size fits all'. Preoperative morbidity, the intraoperative patient condition, and various procedural factors may be important determinants – or effect modifiers – of the IOH treatment threshold. This section will explain which effect modifiers will be considered and the rationale behind that choice (Table 2). The section 'Statistical Analysis' will explain how the effect modifiers are considered during the analysis.

Preoperative morbidity may have a large influence on the blood pressure level at which treatment is initiated. Frail patients are likely to be more vulnerable to the organ hypoperfusion that is caused by IOH. Although numerous factors can contribute to frailty, we aim to restrict the number of preoperative effect modifiers in this study to avoid excessive usage of the data. We expect that age, chronic hypertension and the ASA physical status are the main contributory preoperative effect modifiers and these will be included in the analysis.

The intraoperative condition of the patient may also be a consideration for anesthesia providers to use a different IOH treatment threshold. For instance, when other vital signs are also out of normal ranges, one might consider a higher IOH threshold than when those vital signs are within normal ranges. We will use the average heart rate and the oxygen saturation within 5 minutes after the start of the IOH episode as effect modifiers.

Further, the threshold to treat IOH may depend on preceding IOH. When the blood pressure has been within normal ranges throughout earlier parts of the procedure a low blood pressure may be acceptable. However, prolonged or multiple episodes of IOH that precede the current episode may encourage an anesthesia provider to aim for a higher IOH threshold. The influence of preceding IOH will be studied by separating the analysis for first IOH episodes and subsequent (non-first) IOH episodes. The analysis of subsequent IOH episodes will include both the area under the blood pressure threshold (AUT) during previous IOH episodes and the average blood pressure during previous IOH episodes as effect modifiers.

In addition to the patient condition, progress of the anesthetic case and the surgical procedure may influence which blood pressure thresholds are treated. For example, airway management during induction of anesthesia may be a distraction to the anesthesia providers. Alternatively, prior to the surgical start of the procedure lower blood pressures may be tolerated in anticipation of pain caused by the incision. Therefore, the phase of the procedure (induction / surgical preparation / surgical) will be used as an effect modifier. End of induction will be defined as a textbox option (Case Time 'End of Induction', see Table 4) or five minutes after insertion of a laryngeal mask or endotracheal tube, whichever came first.

The type of procedure may also be a factor for the IOH treatment threshold. Higher IOH thresholds may be considered in patients undergoing vascular surgery, because they may already have preexisting perfusion problems – both localized and systemic. Higher IOH thresholds may also be used during neurosurgical procedures, as the brain is very susceptible to hypoperfusion.

An additional important factor may be blood loss during the procedure. Although blood loss is actively monitored by the surgical and anesthesia teams, it is unlikely that the time at which the bleeding occurred is very accurately documented. Since this study focuses on the timing of IOH treatment, we therefore consider it not feasible to directly use blood loss as an effect modifier in the analysis. Nevertheless, during procedures with ongoing blood loss that impedes the work of the surgeons, the anesthesia providers may choose to accept a lower IOH threshold – i.e. deliberate hypotension. Blood loss may impede surgical progress because of large amounts of ongoing blood loss (e.g. orthopedic and trauma), or small amounts of blood loss in a very delicate surgical field (ENT). Additionally, the risk of blood loss may be higher for prolonged procedures. The duration of surgery, in addition to the type of procedure, will therefore be considered an effect modifier.

Finally, there may be cultural differences between the anesthesia providers of participating centers in their IOH treatment patterns. Therefore, the intracluster correlation and within cluster correlation of the mean time interval between the first hypotensive measurement and onset of blood pressure treatment will be calculated between hospitals. When there is a high intracluster correlation between hospitals, an additional analysis that is stratified on hospitals will be performed (see 'Statistical Analysis' for more details).

IOH = Intraoperative Hypotension; ABP = Arterial Blood Pressure; NIBP = Noninvasive Blood Pressure

Statistical analysis

Continuous variables will be visually assessed for a normal distribution using histograms and qq-plots. Normally distributed data will be presented as means with standard deviations (SD). Non-normally continuous data will be presented as medians with interquartile ranges (IQR). Categorical variables will be expressed as numbers (percentage).

For each IOH threshold (see 'Determinant' for the different types of thresholds) the crude percentage of patients that received a first blood pressure intervention during each minute will be summed and visualized in a histogram with a kernel density line for the entire IOH episode. In other words, a frame will be plotted for all possible blood pressure thresholds with a one mmHg or one percent interval. The x-axis of the plot will range from $t = -5$ through $t = 0$ to $t = 60$ minutes (Figure 2).

The change in the number and timing of blood pressure interventions between the different IOH thresholds may provide an indication of what thresholds are considered to be clinically relevant by the anesthesiologists. These changes will be visualized in a static and a dynamic way.

The static representation will consist of displaying the histograms and density lines for various thresholds. The differences in histograms and density lines between different thresholds for a single threshold type (e.g. differences between absolute systolic thresholds of 90, 80, 70, and 60 mmHg) allows us to see how anesthesiologists respond to specific IOH thresholds. The specific thresholds that will be used for each threshold type is displayed in Table 3.

Table 3 - Thresholds for each type of IOH threshold that will be statically visualized

The changes that occur when lowering thresholds for IOH will be better interpretable when they are dynamically visualized. In other words, an animation that visualizes the changes in the number and timing of interventions when lowering the IOH thresholds. Such an animation will be constructed by inserting the frames for each of the thresholds within a single threshold type into a timeline of a video editing program (see Figure 3). For example, thresholds for absolute systolic blood pressures will run from 150 mmHg to 0 mmHg, providing 151 frames with histograms and density lines. A hypothetical example can be found on [https://youtu.be/C1HsT27rJTA.](https://youtu.be/C1HsT27rJTA)

The secondary outcomes will be visualized in a similar way. However, we expect the required time and effort to render all proposed graphs to be substantial. Therefore, the secondary outcomes will only be visualized when there is a clinically relevant association between the IOH thresholds and the first blood pressure intervention.

Figure 3 - Static representation of the animations that will be used to analyze the relation between the threshold of intraoperative hypotension, its duration and corresponding interventions by physicians.

In addition to the data visualization as described above, the relation between blood pressure and treatment will be modeled using survival models. For each threshold type (SBP and MBP, both relative and absolute) a mixed effects cox proportional hazards model will be estimated with time to the first blood pressure intervention as the dependent variable and the continuous IOH threshold as the independent variable. Although the IOH threshold is a continuous variable it is not expected to have a linear relationship with the outcome variable. The IOH threshold will be entered into the model using restricted cubic splines (number of knots = 3).⁹ A random intercept will be included to account for the multilevel nature of the data – for each threshold type, the time to first intervention is calculated for more than 100 thresholds per patient. The continuous IOH threshold will be included as a fixed effect, as we do not expect the shape of the association between IOH threshold and time to vary considerably between patients. As we test multiple types of thresholds, an alpha < 0.005 will be considered statistically significant. The resulting regression model will be difficult to understand. The resulting regression models provide an estimation of which blood pressures are accepted by anesthesia providers for a particular time – analogous to survival time in a survival analysis. Hence the resulting models do not give a direct answer to which thresholds are not accepted by anesthesia providers. This is also analogous to survival models, as survival models do not distinguish between death and censoring as the reason for the end of survival time. Moreover, the regression parameters will also be difficult to interpret. That's why we will use a graphical representation of the regression

model (an example of such a representation was described in Kappen et al. Anesthesiology 2014).10

Effect modification will be studied in both the visual analysis as well as in the proportional hazards models. The plots and the animations will be stratified according to the proposed effect modifiers in Table 2. For the proportional hazards analysis, each of the variables from Table 2 and their interaction term with the IOH threshold will be added to each of the models. At first, only the variables and their interaction term with the IOH threshold will be added to the models for each variable separately. Then the most important effect modifiers will be selected and combined into a single multivariable model. Because of the large sample size, only using statistical significance to select the most important effect modifiers may not provide appropriate results. The large sample size may cause a clinically irrelevant effect size to be statistically significant. Therefore, effect modifiers will be selected based on a clinically relevant parameter estimate for their interaction term with the IOH threshold, and a reduction of model's AIC (Akaike Information Criterion) by a minimum of two (in comparison with the same model without the effect modifier). Clinically relevant effect modification will be visually assessed using the graphical representation of the proportional hazard model, as described above. We do have some doubts on the feasibility to estimate the full multivariable model. The use of splines for the IOH threshold and several interaction terms with possible effect modifiers may require too much computational time and power.

Management of missing data

For the crude analysis, patients with missing data will be excluded from the analysis. For proportional hazards models, multiple imputation will be used to avoid introducing bias by excluding cases with missing data.

Power analysis

For a sample size of the predictive models that are being used in this study, it has been suggested that the number of events should exceed the number of predictor variables by a factor 10.¹³ Fortunately, blood pressure interventions are common during anesthesia. By including all adult patients under general anesthesia from 2010 – 2015 we expect to have no issues due to a lack of power.

Table 4 - Variables to be collected

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