BMJ Open

Intraoperative haemodynamic optimisation using the Hypotension Prediction Index and its impact on tissular perfusion: a protocol for a randomised controlled trial

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To cite: Lorente JV, Jimenez I, Ripollés-Melchor J, *et al*. Intraoperative haemodynamic optimisation using the Hypotension Prediction Index and its impact on tissular perfusion: a protocol for a randomised controlled trial. *BMJ Open* 2022;**12**:e051728. doi:10.1136/bmjopen-2021-051728

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-051728).

Received 27 March 2021
Accepted 09 May 2022

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ABSTRACT

Introduction Intraoperative arterial hypotension is associated with poor postoperative outcomes. The Hypotension Prediction Index (HPI) developed using machine learning techniques, allows the prediction of arterial hypotension analysing the arterial pressure waveform. The use of this index may reduce the duration and severity of intraoperative hypotension in adults undergoing non-cardiac surgery. This study aims to determine whether a treatment protocol based on the prevention of arterial hypotension using the HPI algorithm reduces the duration and severity of intraoperative hypotension compared with the recommended goal-directed fluid therapy strategy and may improve tissue oxygenation and organ perfusion.

Methods and analysis We will conduct a multicentre, randomised, controlled trial (N=80) in high-risk surgical patients scheduled for elective major abdominal surgery. All participants will be randomly assigned to a control or intervention group. Haemodynamic management in the control group will be based on standard haemodynamic parameters. Haemodynamic management of patients in the intervention group will be based on functional haemodynamic parameters provided by the HemoSphere platform (Edwards Lifesciences), including dynamic arterial elastance, dP/dt_{max} and the HPI. Tissue oxygen saturation will be recorded non-invasively and continuously by using near-infrared spectroscopy technology. Biomarkers of acute kidney stress (cTIMP2 and IGFBP7) will be obtained before and after surgery. The primary outcome will be the intraoperative time-weighted average of a mean arterial pressure <65 mm Hg.

Ethics and dissemination Ethics committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain). Findings will be widely disseminated through peer-reviewed publications and conference presentations.

Trial registration number NCT04301102.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A multicentre randomised controlled trial to test whether an Hypotension Prediction Index-based therapeutical protocol reduces intraoperative hypotension (IOH) and affects tissue oxygenation and organ perfusion in non-cardiac surgery.
⇒ The primary outcome is the intraoperative time-weighted average of the mean arterial blood pressure below 65 mm Hg (TWA- mean arterial pressure<65) and other variables related to IOH. Secondary outcomes are intraoperative S_tO_2, as an indicator of tissue oxygenation, postoperative measurements of the TIMP-2 and IGFBP7 (AKIRisk), postoperative complications, length of hospital stay and 30-day mortality.
⇒ The study sample size was calculated based on the potential reduction in IOH, not the potential reduction in postoperative complications.
⇒ Although the clinical teams performing the trial interventions will not be blinded to the patient inclusion group, they will not be aware of the perioperative StO_2 and AKIRisk variables. Research staff assessing clinical outcomes will not be aware of treatment group assignment.
⇒ No 1-year mortality follow-up of recruited patients is currently proposed.

INTRODUCTION

Intraoperative monitoring of usual haemodynamic parameters, such as heart rate or blood pressure, is insufficient to ensure adequate oxygen delivery (DO_2) to the tissues and prevent organ hypoperfusion.[1] Moreover, tissue hypoxia is a significant determinant of a surgical patient's outcome.[2] Haemodynamic strategies aimed to optimise DO_2 and prevent organ hypoperfusion, also known as

goal-directed therapies (GDT), have been demonstrated to be superior to the traditional care of patients undergoing surgery. This perioperative haemodynamic optimisation has been associated with a significant reduction in morbidity and mortality.[3]

Moreover, arterial hypotension is a frequent phenomenon during the intraoperative period and has been related to the development of organ hypoperfusion and poor postoperative outcomes.[4] Both the duration and severity of arterial hypotension are significant determinants of the postoperative outcome.[5] Particularly, intraoperative hypotension (IOH) significantly increases acute kidney and myocardial injury.[6]

The Hypotension Prediction Index (HPI) is a recently available index developed from machine learning that predicts the occurrence of arterial hypotension from the analysis of the arterial pressure waveform. The HPI value indicates the likelihood of an arterial hypotension event in the following 5–10 min.[7] The use of this index coupled with a proactive therapeutic attitude may reduce IOH in adults undergoing non-cardiac surgery patients.[8–10] However, not all studies that have used intraoperative HPI-guided therapy have successfully reduced the time and severity of IOH. Particularly, the pilot study by Maheshwari *et al*[11] did not demonstrate a significant reduction in IOH using an HPI-guided therapeutical protocol. Furthermore, all these positive results came from single-centre studies or retrospective analysis of available data, which reduces the external validity of their results.

Moreover, since tissue oxygenation depends not only on DO_2 but also on perfusion pressure, haemodynamic optimisation should be targeted to achieve an adequate blood flow and arterial pressure that ensures normal organ function. We, therefore, hypothesise that an HPI-based therapeutic protocol will reduce the overall duration of intraoperative arterial hypotension and may improve tissue oxygenation and organ perfusion during non-cardiac surgery.

METHODS AND ANALYSIS

This manuscript was written according to the Standard Protocol Items: Recommendations for Interventional Trials guideline (online supplemental file 1) on reporting of interventional trial protocols.[12]

A multicentre, randomised controlled trial, with daily follow-up of patients until hospital discharge and mortality censured at 30 days after surgery, will be conducted. The study will be carried out at five different Spanish hospitals: Juan Ramón Jiménez University Hospital (Huelva), Virgen del Rocío University Hospital (Sevilla), Infanta Leonor University Hospital (Madrid), Hospital Universitario SAS de Jerez (Jerez de la Frontera) and Infanta Cristina University Hospital (Badajoz).

Enrolled patients will be at least 65 years old and/or American Society of Anesthesiologist (ASA) physical status III/IV, scheduled for elective major abdominal surgery (general surgery, urology, or gynaecology, through laparoscopic or open approach), with general or combined anaesthesia. Surgery will be considered to be major if the expected duration is >2 hour, or the estimated blood loss is >15% of blood volume, or if the expected required transfusion is ≥2 packed red blood cells.

Exclusion criteria will be pregnancy, preoperative glomerular filtrate <60 mL/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 formula, persistent atrial fibrillation, known cardiac shunts, right ventricular dysfunction, severe valvulopathy, kidney transplant recipient and refusal to participate in the study.

Study protocol

Researchers will screen all patients who present for elective, non-cardiac surgery. Patients will be contacted by the principal investigator (PI) of each hospital and informed if they are eligible. The patient's informed consent will be obtained the day before surgery. Patient demographics and comorbidities will be collected before randomisation. Patients will be assigned by the local PI to the intraoperative HPI algorithm (intervention group) or a GDT algorithm (control group). We will use a computer-generated, variable block randomisation method through age strata. Patients will not be aware of the group allocation. Although intraoperative personnel (anaesthesiologists, surgeons…) will be not blinded to monitoring allocation, data-analysis will remain blinded.

All PIs and collaborators will receive specific training with the monitoring used for haemodynamic management.

A Consolidated Standards of Reporting Trials flow diagram of the study is shown in figure 1. All data will be entered using an electronic Clinical Report Form in Castor EDC, a Good Clinical Practice compliant data management system.[13]

Common perioperative measures

Before the induction and during surgery, all subjects will receive standard of care with a five-lead ECG, pulse oximetry, a peripheral intravenous line and an indwelling radial arterial catheter.

All subjects will receive general or combined anaesthesia, neuraxial analgesia technique (epidural or intradural) will be performed according to the preference of the anaesthesiologist before induction. For pragmatic reasons, the administration of the drugs used in the induction of anaesthesia and neuromuscular relaxants will be at the discretion of the anaesthesiologist. Bispectral-index monitoring (BIS; Medtronic, Dublin, Ireland) will be used to monitor the depth of anaesthesia. Sevoflurane will be used for hypnosis maintenance, with a BIS target range of 40–60. All patients will receive invasive and continuous arterial pressure monitoring with an indwelling radial arterial catheter connected to a FloTrac sensor in the control group or an Acumen IQ sensor in the intervention group (Edwards Lifesciences, Irvine, California, USA).

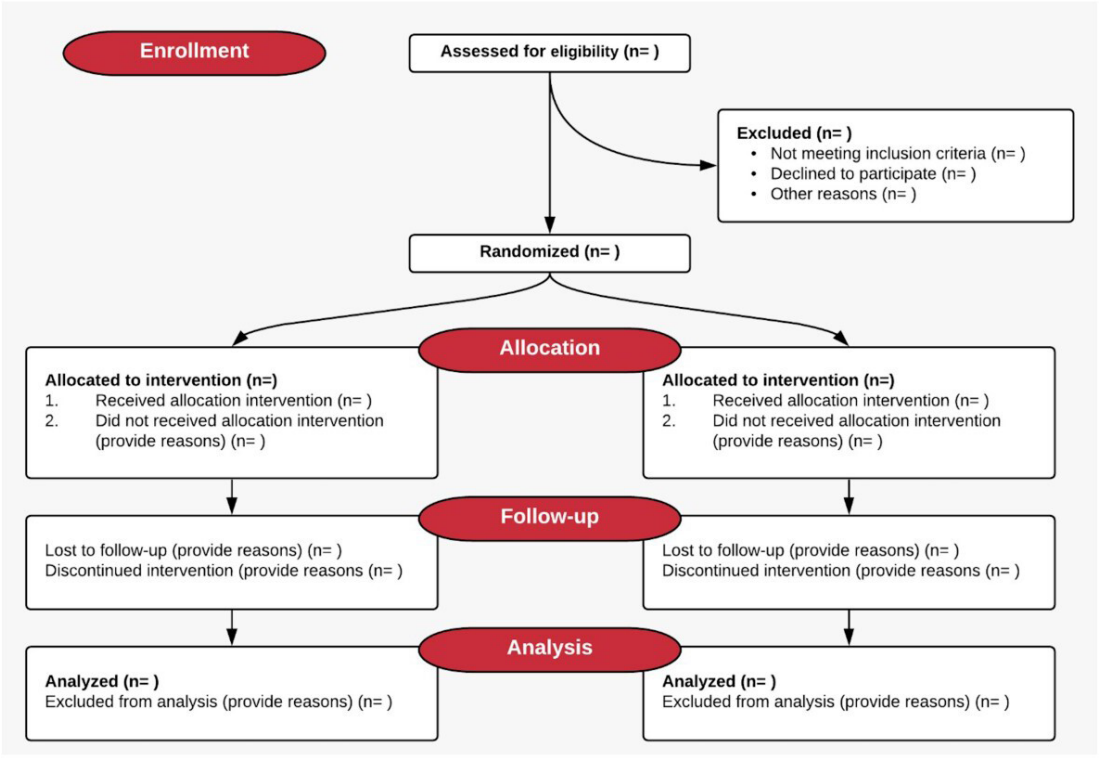

Figure 1 CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials.

All subjects will receive standard measures to maintain oxygen saturation by pulse oximetry >94%, normothermia (>36°C) and heart rate <100 beats/min. Ventilation with an inspired oxygen fraction of 60% will be mechanically controlled to maintain $PaCO_2$ between 4.7 and 6.0 kPa, with a positive end-expiratory pressure of 4–6 mm Hg and a tidal volume of 8 mL/kg. For maintenance fluid therapy, a balanced crystalloid (Isofundin/Plasmalyte) will be administered at 1–3 mL/kg/hour for laparoscopic surgery and 5–7 mL/kg/hour for open surgery. Flow optimisation will be performed with hydroxyethyl starch (Voluven).[14] Packed red blood cells will be transfused if the haemoglobin level is <80 g/L.[15] The choice and dose of the vasopressor and ionotropic drugs will be determined by the anaesthesiologist in charge of the patient in both groups.

Tissue oxygen saturation (StO_2) will be non-invasively and continuously recorded every 2 s placing an adult sensor (ForeSight Elite sensor, model FSESL, Edwards Lifesciences) over the brachioradial muscle by using near-infrared spectroscopy (NIRS) technology (ForeSight Elite tissue oximetry system, Edwards Lifesciences=). Details about this NIRS technology are provided elsewhere.[16] StO_2 values will be hidden from the main screen in both groups but will be recorded internally into the HemoSphere system, so StO_2 values will not be available to clinicians and therefore cannot induce changes in patient management.

The haemodynamic optimisation algorithm will begin 15 min after the start of the surgery, once the haemodynamic impact of anaesthesia and surgery have been stabilised. Meanwhile, the haemodynamic goal in both groups will be to achieve a mean arterial pressure (MAP) >65 mm Hg with the administration of boluses of vasopressors at the choice of the anaesthesiologist. In both groups, haemodynamic data will be recorded every 20 s in the HemoSphere system after starting the haemodynamic optimisation protocols and downloaded after the surgery for offline analysis.

During the surgery, any procedure carried out with repercussions for the haemodynamic status of the patient will be marked and adequately labelled for further identification.

Biomarkers of acute kidney stress in the perioperative period will be measured by the PI and blinded for the rest of the researchers. Urinary (TIMP-2)-(IGFBP7) will be measured with the Astute140 Meter (BioMérieux). This device applies a sandwich immunoassay technique and converts the fluorescent signals from each of the two immunoassays (TIMP-2 and IGFBP7) contained within the Nephrocheck test cartridge into a single numerical risk result (AKIRisk). The result is calculated as the product of the measured concentrations of the two cell-cycle arrest biomarkers and can quantify the stress developed by kidney epithelial cells during surgery, identifying patients at risk of postoperative acute kidney injury (AKI).[17–19]

The first urine sample will be collected when performing the bladder catheterisation after induction. The first postoperative sample will be collected 4 hours after the patient's admission to the Intensive Care Unit for postoperative stay. If the value of this sample is in the grey zone,

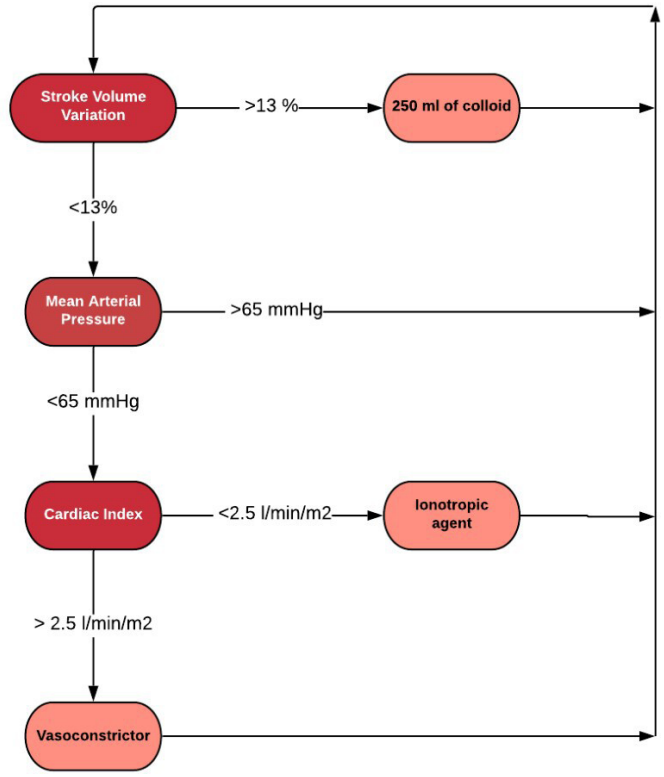

Figure 2 Control group haemodynamic optimisation algorithm.

between 0.3 and 2, a second postoperative sample will be collected 12 hours after the first one.[20]

Arterial blood analyses will be performed after induction of anaesthesia, midway through the surgery, immediately after admission to the intensive care unit, and daily from postoperative day 1–day 5 inclusive.

Haemodynamic management

Control group

Haemodynamic management will be based on the haemodynamic parameters provided by the HemoSphere platform with the FloTrac sensor, including cardiac index (CI) and stroke volume variation (SVV). The haemodynamic optimisation algorithm on this group is shown in figure 2. If SVV increases above 13%, a fluid bolus of 250 mL of colloid will be performed. MAP will be maintained above 65 mm Hg by a vasoconstrictor drug. An ionotropic agent will be added if the CI persists <2.51/mL/m^2 after previous steps.

Intervention group

Haemodynamic management will be based on the haemodynamic parameters provided by the HemoSphere platform with the Acumen IQ sensor, including CI, SVV and Acumen IQ specific parameters: maximum arterial pressure rise (dP/dt_{max}), dynamic arterial elastance (Ea_{dyn}) and HPI. The haemodynamic optimisation algorithm on the intervention group is based on the three main mechanisms leading to arterial hypotension: hypovolaemia, impaired contractility and vasoplegia (figure 3). When HPI rises above 85, SVV will be checked. If SVV is <13%,

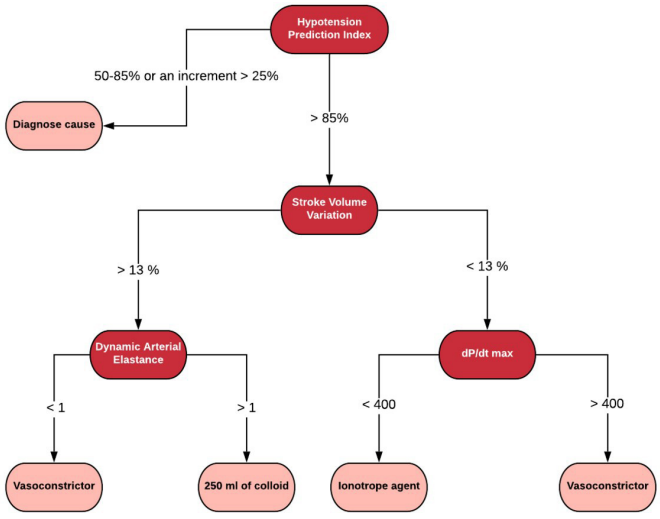

Figure 3 Intervention group haemodynamic optimisation algorithm.

a vasoconstrictor will be administered if dP/dt_{max} value is >400 mm Hg·s, or an inotrope if dP/dt_{max} is <400 mm Hg·s. If SVV is >13%, a 250 mL fluid bolus will be administered if the Ea_{dyn} value is >1, or a vasoconstrictor if Ea_{dyn} <1.

Study outcomes

Primary outcomes

Intraoperative time-weighted average of MAP <65 mm Hg (TWA-MAP <65), calculated as the area between 65 mm Hg threshold and the curve of the MAP measurements (AUC 65 mm Hg) divided by the total continuous reading time:[21]

$$TWA-MAP<65=\frac{\sum_{i=1}^{k}(area_1\ 65)+(area_2\ 65+\ldots+area_k\ 65)}{Total\ time\ of\ measurements}$$

The advantage of using TWA-MAP instead of MAP is that the former combines the severity and duration of the hypotension considering the overall duration of the surgery.

Other variables related to IOH: the number of IOH episodes (defined as an event of MAP <65 mm Hg of at least 1 min duration) and the total time of hypotension per case.

Secondary outcomes

The secondary outcomes include:

- Intraoperative StO_2, as an indicator of tissue oxygenation and wellness of the microcirculation. StO_2 will be non-invasively and continuously recorded in the brachioradial muscle in the arm opposite to the arterial line. We will calculate the time-weighted average of all StO_2 measurement values, the time weighted averaged below an individual specific threshold obtained during the first minute of optimisation and identifying the minimum StO_2, defined as the minimum value sustained at least for 5 min.[22 23]
- Postoperative measurements of the TIMP-2 and IGFBP7 (AKIRisk). We will compare the AKIRisk at baseline and the evolution among both groups.

	STUDY PERIOD				
	Enrolment	Study Intervention			
TIMEPOINT**	d_{-1}	Surgical day (d_0)	Daily follow-up (d_1-d_{hd})	Hospital discharge (d_{hd})	Follow-up (d_{30})
ENROLMENT:					
Eligibility screen	X				
Written and oral project explanation	X				
Written Informed consent	X				
Allocation		X			
Patient demographic/comorbidities	X	X			
INTERVENTIONS:					
Control group		X			
Intervention group]		X			
ASSESSMENTS:					
Primary outcomes		X			
Secondary outcomes		X	X	X	X

Figure 4 Schedule of enrolment, interventions and assessments. ** Specific timepoints listed

At the end of the surgery, data regarding the total fluid therapy during surgery, the accumulated dose of opioids during the intraoperative period, accumulated dose of vasoactive agents during the intraoperative period, accumulated dose of ionotropic drugs during the intraoperative period, other drugs with a haemodynamic impact not included in previous groups, total intraoperative diuresis, and transfusion of total blood products during surgery, will be collected.

Secondary outcomes will also include postoperative complications in accordance with the European Perioperative Clinical Outcome definitions,[24] length of hospital stay and 30-day mortality. Postoperative follow-up of patients will be performed by a collaborating investigator from each centre, blinded for the randomisation. For an overview of the outcome assessments, see figure 4.

Sample size and data analysis

The literature indicates that a cumulative hypotension time of more than 10 min during surgery is clinically relevant.[25] Given the novelty of the HPI parameter and the lack of publications during the design of this study, a pilot study in 31 patients undergoing major surgery was performed at the Virgen del Rocío Hospital. In this preliminary study, two groups were defined: a control group with invasive and continuous arterial pressure monitoring but without the use of HPI; and an intervention group with invasive and continuous blood pressure monitoring, in which the anaesthesiologist also had access to the HPI value and the additional parameters during surgery. In both groups, the haemodynamic objective during the intraoperative period was to maintain the MAP above 65 mm Hg. The results from this preliminary study revealed that in the control group (15 patients), 68.75% of the patients accumulated more than 10 min of hypotension (11 patients), while in the intervention group with HPI (16 patients), only 31.25% of the patients accumulated periods of a MAP <65 mm Hg more than 10 min (5 patients).

Based on this pilot study, to achieve a 90% power, and a significance level of 5%, 72 patients will be required (36 in each group). Assumed a drop-out rate of 10%, a total of 80 patients will be required (40 patients per group).

Statistical analysis

The normality of data distribution was assessed by the D'Agostino-Pearson test and confirmed by inspection of a Q-Q Plot. The results are expressed as the mean±SD when normally distributed or the median (25th–75th IQR). Categorical data were given as frequencies with percentages.

Comparison of quantitative variables between control and intervention group will be performed with the Mann-Whitney U test or the independent *t* test, and the χ^2 test for categorical variables. To establish a relationship between changes IOH management and tissue perfusion, a regression analysis will be performed between TWA-MAP and the perfusion indexes (StO_2 and AKIRisk).

A $p<0.05$ will be considered statistically significant. The statistical analyses will be performed with the SPSS software, V.23.0.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION

Our goal is to determine whether a goal-directed algorithm based on the prevention of arterial hypotension using the HPI and the aid of the additional parameters, such as arterial dP/dt_{max} and Ea_{dyn}, reduces the duration and severity of IOH when compared with the recommended goal-directed fluid therapy. We also aim to determine whether this optimisation of the systemic perfusion pressure influences intraoperative tissue perfusion and postoperative complications. To achieve this objective, we will include patients with a higher risk of IOH (>65 years old and/or ASA III/IV).

Considering the significant impact of intraoperative arterial hypotension on mortality and morbidity, arterial pressure should be considered as a critical element. Therefore, maintaining blood pressure within a physiological range that ensures tissue perfusion should be considered not an option. Furthermore, the definition of blood pressure as a critical element, also implies a paradigm shift in the current treatment of intraoperative arterial hypotension from a reactive attitude to a proactive action based on predictors, such as HPI. If this proactive attitude associates with a better patient's outcome still needs to be proven clinically. Moreover, the proper correction of arterial hypotension also depends on the adequate identification of the pathophysiological mechanisms leading to low

blood pressure and the choice of the optimal treatment.[9] Accordingly, the clinical benefit of an artificial parameter based on machine learning, such as HPI, should be analysed coupled with the haemodynamic protocol that determines the best treatment according to those physiological mechanisms involved in the development of arterial hypotension. Therefore, if this preemptive haemodynamic protocol affects tissue perfusion is also one of the main goals of our study.

ETHICS AND DISSEMINATION

Ethics Committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain). Written informed consent will be obtained from all included patients. Patients will be informed that they may decline to participate or withdraw from the study at any time.

Serious adverse effect of the product which, by its nature, incidence, intensity or consequences has not been identified in the updated version of the risk analysis report.

Regardless of the outcomes, it is our intention to publish the results of this study in a peer-reviewed journal. Findings will also be presented at Spanish and international conferences.

Trial status

Protocol V.1.0; March 2020. Recruitment started in November 2020, and it is expected to be finished on February 2022.

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Funding This study was supported by Edwards Lifesciences through a grant provided after presenting the study to a competitive international call via its Grant Portal (Grant Number: HCP-8200579).

Disclaimer The design of the study, the writing of this manuscript and the collection and interpretation of data are being carried out independently by the research team, without any intervention from the funding body.

Competing interests JVL: Edwards Lifesciences, Fresenius Kabi, Baxter, Vifor Pharma and bioMérieux conference fees, financial support for Edwards Lifesciences research obtained through the Grant Portal of the company. Economic research support from bioMérieux. IJ: Edwards Lifesciences conference fees. JR-M: Edwards Lifesciences, MSD, Fresenius Kabi and Dextera Medical conference fees. MIM: Clinical consultant for Edwards Lifesciences and Dextera Medical. WW: Employed by Edwards Lifesciences. The rest of the authors declare no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. *Crit Care Med* 1988;16:1117–20.
2 Parker T, Brealey D, Dyson A, *et al*. Optimising organ perfusion in the high-risk surgical and critical care patient: a narrative review. *Br J Anaesth* 2019;123:170–6.
3 Heming N, Moine P, Coscas R, *et al*. Perioperative fluid management for major elective surgery. *Br J Surg* 2020;107:e56–62.
4 Ahuja S, Mascha EJ, Yang D, *et al*. Associations of intraoperative radial arterial systolic, diastolic, mean, and pulse pressures with myocardial and acute kidney injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology* 2020;132:291–306.
5 Walsh M, Devereaux PJ, Garg AX, *et al*. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013;119:507–15.
6 Khanna AK, Maheshwari K, Mao G, *et al*. Association between mean arterial pressure and acute kidney injury and a composite of myocardial injury and mortality in postoperative critically ill patients: a retrospective cohort analysis. *Crit Care Med* 2019;47:910–7.
7 Hatib F, Jian Z, Buddi S, *et al*. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. *Anesthesiology* 2018;129:663–74.
8 Wijnberge M, Geerts BF, Hol L, *et al*. Effect of a machine Learning-Derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: the hype randomized clinical trial. *JAMA* 2020;323:1052–60.
9 de Keijzer IN, Vos JJ, Scheeren TWL. Hypotension prediction index: from proof-of-concept to proof-of-feasibility. *J Clin Monit Comput* 2020;34:1135–8.
10 Schneck E, Schulte D, Habig L, *et al*. Hypotension prediction index based protocolized haemodynamic management reduces the incidence and duration of intraoperative hypotension in primary total hip arthroplasty: a single centre feasibility randomised blinded prospective interventional trial. *J Clin Monit Comput* 2020;34:1149-1158.
11 Maheshwari K, Shimada T, Yang D, *et al*. Hypotension prediction index for prevention of hypotension during moderate- to high-risk noncardiac surgery. *Anesthesiology* 2020;133:1214–22.
12 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586–42.

13 EDC C. Castor electronic data capture., 2019. Available: https://castoredc.com
14 Chappell D, van der Linden P, Ripollés-Melchor J, *et al*. Safety and efficacy of tetrastarches in surgery and trauma: a systematic review and meta-analysis of randomised controlled trials. *Br J Anaesth* 2021;127:556–68.
15 Kozek-Langenecker SA, Ahmed AB, Afshari A. *Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology*. , 2017: 34, 332–95.
16 Scheeren TWL, Schober P, Schwarte LA. Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications. *J Clin Monit Comput* 2012;26:279–87.
17 Kashani K, Al-Khafaji A, Ardiles T, *et al*. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 2013;17:R25.
18 Meersch M, Schmidt C, Hoffmeier A, *et al*. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med* 2017;43:1551–61.
19 Gocze I. Biomarker-Guided intervention to prevent acute kidney injury the prospective randomized BigpAK study. *Ann Surg* 2017;267:1–8.
20 Engelman DT, Crisafi C, Germain M. Utilizing urinary biomarkers to reduce acute kidney injury following cardiac surgery. *J Thorac Cardiovasc Surg* 2020.
21 Maheshwari K, Khanna S, Bajracharya GR, *et al*. A randomized trial of continuous noninvasive blood pressure monitoring during noncardiac surgery. *Anesthesia & Analgesia* 2018;127:424–31.
22 Abdelmalak BB, Cata JP, Bonilla A, *et al*. Intraoperative tissue oxygenation and postoperative outcomes after major non-cardiac surgery: an observational study. *Br J Anaesth* 2013;110:241–9.
23 Spruit RJ, Schwarte LA, Hakenberg OW, *et al*. Association of intraoperative tissue oxygenation with suspected risk factors for tissue hypoxia. *J Clin Monit Comput* 2013;27:541–50.
24 Jammer I, Wickboldt N, Sander M, *et al*. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European perioperative clinical outcome (EPCO) definitions: a statement from the ESA-ESICM joint Taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015;32:88–105.
25 Wesselink EM, Kappen TH, Torn HM, *et al*. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth* 2018;121:706–21.