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Evaluation of the early use of norepinephrine in major abdominal surgery on medical and surgical postoperative complications: study protocol for a randomised controlled trial (EPON STUDY)

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ABSTRACT

Background Post-induction anaesthesia often promotes intraoperative hypotension (IOH) that can worsen postoperative outcomes. This study aims to assess the benefit of norepinephrine versus ephedrine at the induction of anaesthesia to prevent postoperative complications following major abdominal surgery by preventing IOH.

Methods and analysis The EPON STUDY is a prospective single-centre randomised controlled trial with the planned inclusion of 500 patients scheduled for major abdominal surgery at the Amiens University Hospital. The inclusion criteria are patients aged over 50 years weighing more than 50 kg with an American Society of Anesthesiologists physical status score of ≥2 undergoing major abdominal surgery under general anaesthesia. Patients are allocated either to the intervention group (n=250) or the standard group (n=250). In the intervention group, the prevention of post-induction IOH is performed with norepinephrine (dilution to 0.016 mg/mL) using an electric syringe pump at a rate of 0.48 mg/h (30 mL/h) from the start of anaesthesia and then titrated to achieve the haemodynamic target. In the control group, the prevention of post-induction IOH is performed with manual titration of ephedrine, with a maximal dose of 30 mg, followed by perfusion with norepinephrine. In both groups, the haemodynamic target to maintain is a mean arterial pressure (MAP) of 65 mm Hg or 70 mm Hg for patients with a medical history of hypertension. An intention-to-treat analysis will be performed. The primary outcome is the Clavien–Dindo score assessed up to 30 days postoperatively. The secondary endpoints are the length of hospital stay and length of stay in an intensive care unit/postoperative care unit; postoperative renal function; postoperative cardiovascular, respiratory, neurological, haematological and infectious complications at 1 month; and volume of intraoperative vascular filling and mortality at 1 month.

Ethics and dissemination Ethical approval was obtained from the committee of protection of the persons of Ile de France in May 2021 (number 21 05 41). The authors will be involved in disseminating the research findings (through attending conferences and co-authoring papers). The results of the study will be disseminated via peer-reviewed publications and presentations at national and international conferences.

Trial registration number NCT05276596.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ According to the arm allocation, patients will receive either pre-emptive norepinephrine before the occurrence of arterial hypotension or curative ephedrine if intraoperative arterial hypotension occurs (gold standard care).
⇒ The primary endpoint will be surgical outcomes assessed at 1 month from surgery using the Clavien–Dindo score (validated score).
⇒ The main limitation is the single-centre design, which restricts generalisation.

INTRODUCTION

In major abdominal surgery, the incidence of intraoperative hypotension (IOH) remains high. The reasons are multifactorial and are associated with major postoperative complications, including acute kidney injury, myocardial injury and death.[1 2] There are multiple surgical causes, but anaesthetic drugs are also a major source of hypotension. Indeed, anaesthetic drugs are known for their depressive effect on the cardiocirculatory system and cause hypotension from the outset of anaesthesia. Pharmacologically, hypnotic drugs induce depression of the baroreflex, sympathetic inhibition, a decrease in the secretion of endogenous norepinephrine

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and epinephrine and, thus, a decrease in vascular resistance with vasodilatation. This, in turn, causes a decrease in venous return and, consequently, the cardiac preload.[3] This effect is more pronounced for patients with risk factors such as preoperative high blood pressure, cardiovascular or respiratory diseases, cancer or chronic renal or hepatic failure.[4] There is no uniform definition for IOH.[5 6] Currently it is unknown whether IOH should be defined based on absolute thresholds or relative thresholds based on the decrease from baseline arterial blood pressure.[7] Frequently, hypotension is defined as systolic blood pressure of <90 mm Hg or mean blood pressure of <65 mm Hg. In routine clinical practice, hypotension after anaesthetic induction is first treated with the administration of ephedrine. Norepinephrine is a second-line treatment. Administration of norepinephrine leads to an increase in cardiac preload, without an increase in afterload. This results in an increase in cardiac output, whereas ephedrine favours an increase in cardiac output, despite a greater increase in cardiac afterload. It leads to the development of potentially deleterious tachycardia for the patient. In addition, the efficiency of ephedrine can vary. Therefore, norepinephrine may be a more appropriate option for maintaining blood pressure with fewer adverse effects on the heart rate.[8] Crystalloid fluid overload has also been shown to favour postoperative complications of abdominal surgery.[9 10] Fluid retention through the preventive use of norepinephrine could therefore be beneficial. In recent years, several teams have proposed the evaluation of norepinephrine as a first-line drug before the occurrence of hypotension during major abdominal surgery.[11] Thus, in obstetrics, the preventive use of norepinephrine for caesarean sections performed under spinal anaesthesia was shown to be associated with a reduction in the incidence of IOH without any deleterious effects for the newborn or parturient. However, no study has demonstrated its benefit in terms of surgical complications in abdominal surgery. We hypothesised that the preventive use of norepinephrine in major abdominal surgery reduces postoperative medicosurgical complications, evaluated by the Clavien–Dindo score, and postoperative organ dysfunction.

METHOD AND ANALYSIS

Study design

This is a randomised, parallel group, open-label, single-centre, superiority trial. The study protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines.[12]

Study population

The inclusion criteria are as follows:

- Patients scheduled for major abdominal surgery (defined as surgery with a risk of cardiovascular complications of >1%[13] and/or lasting more than 2 hours) with general anaesthesia.
- American Society of Anesthesiologists physical status (ASA-PS) score of ≥2.
- Age of ≥50 years and weighing more than 50 kg
- Written informed consent.

The exclusion criteria are as follows:

- Emergency surgery.
- Untreated or uncontrolled hypertension (systolic blood pressure of >150 mm Hg), despite medication.
- Any acute cardiovascular event, including acute or decompensated heart failure or acute coronary syndrome.
- Patients with chronic kidney disease with a glomerular filtration rate of <30 ml.min^{-1}/1.73 m^2 or requiring renal replacement therapy for end-stage renal disease.
- Patients with severe hepatic failure (ASAT/ALAT of >2N, elevated bilirubin level, PT of <50%).
- Preoperative sepsis, septic shock.[14]
- Preoperative norepinephrine infusion.
- Patients eligible for a surgical procedure under locoregional anaesthesia.
- Pregnancy.
- Known allergy to study treatment.
- Patients unable to give informed consent for any reason.

Study protocol

Randomisation

Patients are randomised into two parallel open-label groups. Randomisation is performed using computer-generated block randomisation (Ennov Clinical software). It consists of a list of randomisation with fixed-size random blocks stratified on the anaesthetic induction drug (etomidate or propofol). The results of the randomisation are displayed as the 'control group' or 'intervention group' (figure 1).

Blinding

Trial participants and anaesthesiologist are aware of the patient allocation group. The evaluator of the primary endpoint was blinded.

Standard procedures and definition of IOH

Anaesthesia induction proceeds with a combination of a hypnotic drug (etomidate or propofol), an opioid drug (sufentanil) and a curare (cisatracurium, atracurium or rocuronium). The choice of hypnotic drug is at the discretion of the physician. The combination of locoregional anaesthesia (peripheral nerve block or perimedullar anaesthesia) with general anaesthesia is allowed. Before induction, preoxygenation is carried out using a facial mask until an end-tidal oxygen fraction of 90% is reached. Blood pressure is monitored every 2 min. After induction, all patients are continuously monitored for stroke volume and blood pressure trough using a radial artery line. Intraoperative fluid management is managed according to French guidelines, with the administration of 250 mL Ringer lactate when the change in stroke volume is >15%, with an increase in stroke volume

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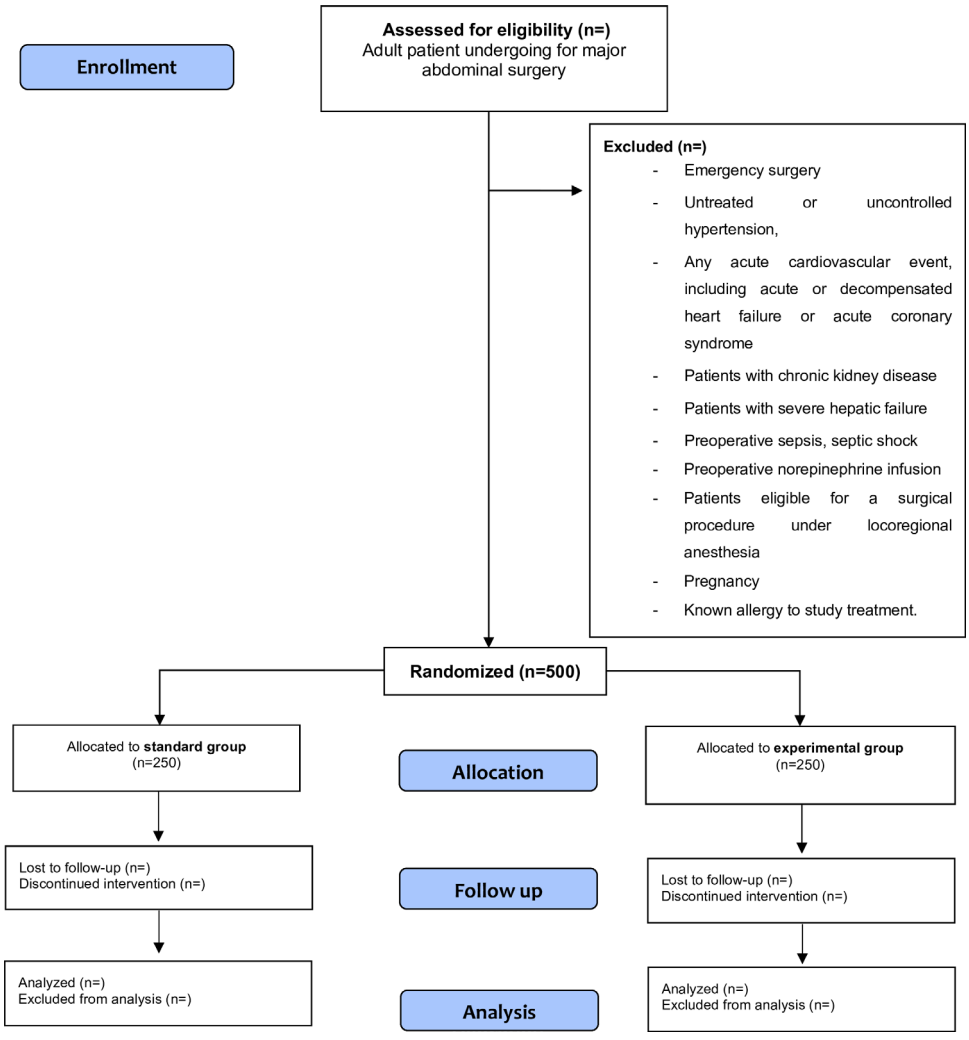

Figure 1 Consolidated Standards of Reporting Trial diagram.

defining the responders.[15] An antiemetic drug is administered at induction (8 mg dexamethasone). After orotracheal intubation, mechanical ventilation is started with a tidal volume of 8 mL/kg ideal body weight, a positive end-expiratory pressure of 5 cmH_2O, a respiratory rate to obtain an end-tidal CO_2 between 35 and 40 mm Hg and an oxygen fraction to target oxygen saturation of >95%. The depth of anaesthesia is monitored with a bispectral index target between 40 and 60. No pre-induction fluid infusion was planned in the study.

The induction period is defined as the time from the start of induction to the surgical incision. During the induction period, a MAP of <65 mm Hg or <70 mm Hg for patients with a medical history of hypertension is defined as IOH.

Intervention group

In the intervention group, continuous intravenous injection of norepinephrine (0.016 $mg.ml^{-1}$) is started at a rate of 0.48 $mg.h^{-1}$ from the induction of anaesthesia. Titration is performed to maintain a MAP of 65 or 70 mm Hg for patients with a medical history of hypertension. An episode with a MAP of >160 mm Hg is considered a hypertensive episode and declared as an adverse event and notified in the data collection.

Standard group

In the standard group, IOH is managed with iterative boluses of ephedrine (3 mg/mL) to a maximum dose of 30 mg. The haemodynamic goal is to maintain a MAP of 65 or 70 mm Hg for patients with a medical history of hypertension. If the goal is not achieved, continuous intravenous injection of norepinephrine (0.016 $mg.ml^{-1}$) is started (figure 2).

Outcome measures

Primary outcome

The primary outcome is the occurrence of postoperative medicosurgical complications within 30 days postoperatively. The primary endpoint is assessed using the Clavien–Dindo surgical score[16 17] (table 1). This score is evaluated postoperatively on day 30. The therapy used to correct a specific complication is the basis of this classification to rank complications in an objective and reproducible manner. It consists of seven grades (I, II, IIIa, IIIb, IVa, IVb and V).

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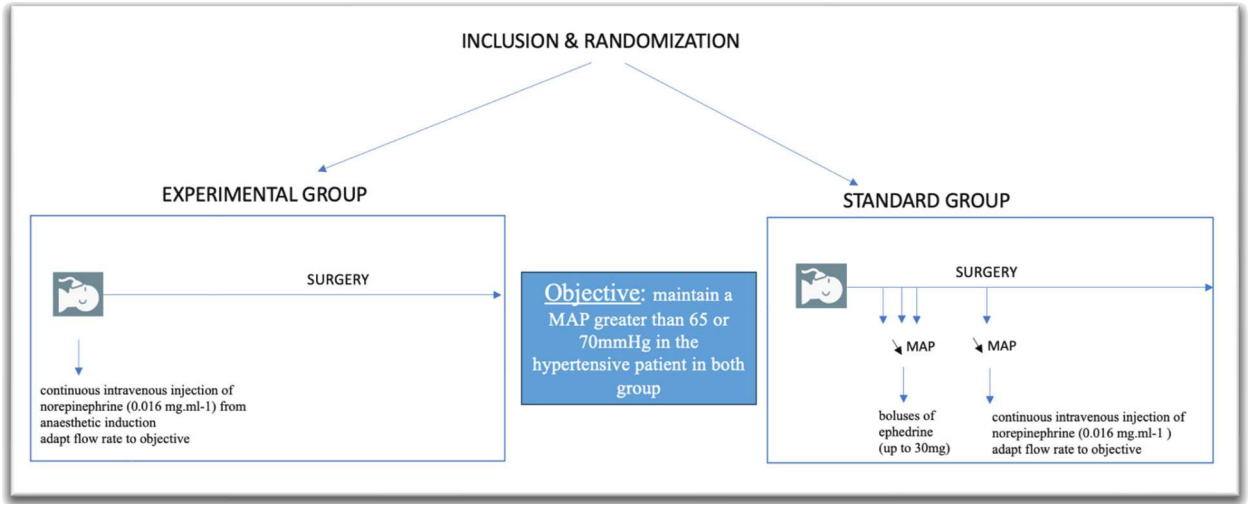

Figure 2 Study protocol. MAP, mean arterial pressure

Secondary outcomes

- Length of hospital stay and length of intensive care unit/postoperative care unit stay.
- Postoperative renal function assessed by the KDIGO score at 48 hours.[18]
- Postoperative cardiovascular complications: persistent circulatory shock defined by the use of vasoactive drugs beyond the 12th hour postoperatively, cardiac rhythm disorder or acute coronary syndrome recorded at 48 hours, 7 days, or 1 month postoperatively.
- Postoperative respiratory complications: respiratory infection,[19] atelectasis, oxygen support, mechanical ventilation or non-invasive ventilation or acute respiratory distress syndrome (ARDS)[20] at 48 hours, 7 days or 1 month postoperatively.
- Infectious complications: sepsis and septic shock as defined in the international definitions (sepsis-related organ failure assessment score) (14) at 48 hours, 7 days or 1 month postoperatively.
- Neurological complications: altered consciousness, stroke at 48 hours, 7 days or 1 month postoperatively.
- Haematological complications: intraoperative blood loss, blood transfusion and haemostasis disorder at 48 hours or 7 days.
- The volume of intraoperative fluid therapy.
- Evaluation of the level of dependence in the activities of daily living (IADL scale)[21] at 1 month post-discharge from the hospital.

Data collection and inclusion visits

The following data are collected: age (years), gender, body mass index ($kg.m^{-2}$), medical and surgery history (cardiovascular risk factors, coronary disease, stroke, cirrhosis, cancer, diabetes, chronic kidney disease, chronic obstructive pulmonary disease), usual medication, surgery type and baseline blood test (blood count, ionogram, urea, creatinine, coagulation test).

Table 1 Clavien–Dindo surgical score

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiological interventions. Allowed therapeutic regimens are drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
IIIA	Intervention not under general anaesthesia
IIIB	Intervention under general anaesthesia
Grade IV	Life-threatening complications requiring ICU management
IVA	Single organ dysfunction (including dialysis)
IVB	Multiorgan dysfunction
Grade V	Death of a patient

Extra suplemmentary file: Patient written consent form.
ICU, intensive care unit.

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Intraoperatively, we collect the systolic, diastolic and mean blood pressure; cardiac output; and stroke volume 10 min after the induction of anaesthesia and then every 30 min until the end of surgery. Extraction of blood pressure elecotronic records will proceed to assess the trend in blood pressure and to estimate the number of IOH. Vascular fluid therapy, monitored at the end of surgery and the cumulative dose of vasoactive drugs and the duration of surgery are also recorded.

Blood tests include those for arterial blood gases (pH, PaO_2, $PaCO^2$, lactate, HCO_3), sodium, potassium, chlorine, urea, creatinine, cardiac troponin, blood counts (haemoglobin, platelets) and coagulation (prothrombin time, activated partial thromboplastin time, fibrinogen) performed 2 hours after the surgical incision and then immediately postoperatively. These tests are also performed 3 and 7 days after the patient's inclusion in the study.

There is an inclusion visit on days 3 and 7 to assess the endpoints and screen for adverse events. A clinical examination is performed at this time to check for postoperative complications (cardiovascular, respiratory, infectious, neurological or haematological).

The last inclusion visit occurs on day 30 with a phone call to assess the endpoints and IADL scale (instrumental activities of daily living).

Data transfer to the case report forms is solely performed by the local investigator and trial physicians to promote data quality and is reviewed by the project leader.

Intention-to-treat analysis

All patients are analysed according to their assigned group following the intention-to-treat principle.

Statistical method and sample size calculation

The medico-surgical complication rate found in the literature is between 25% and 30%.[22]

Thus, if we set the rate of medical and surgical complications (defined by a Clavien–Dindo score of ≥1) to 25% in the control group, the inclusion of 500 patients (250 in each arm) would show a 10% difference between the two groups, with a two-sided first-species risk of 5% and a power of 80%, and an expected loss to follow-up of 5%.

The main objective of this randomised controlled trial is to demonstrate the efficacy of the preventive use of norepinephrine in major abdominal surgery on the occurrence of postoperative medico-surgical complications. Patients are randomised into two groups, with stratification based on the anaesthetic induction drug (etomidate or propofol): control group or immediate norepinephrine perfusion.

All statistical analysis will be performed on an intention-to-treat basis using SAS software version 9.4.

Analysis of the primary endpoint

The primary outcome will be reported as 'intention to treat'. The null hypothesis (the occurrence of postoperative medico-surgical complications is identical between the two arms) will be rejected in favour of the alternative hypothesis (there is a difference) using a univariate logistic regression model with a two-sided first-species risk of 5%.

The difference between the two arms will be validated after adjustment for the type of anaesthetic induction drug with a multivariate logistic regression model.

Results will be presented two-tailed and a p value of <0.05 will be considered significant.

Analysis of secondary endpoints

Quantitative variables will be compared between the two arms using Student's t-test for independent samples or the Mann–Whitney test, depending on the normality of the data. Qualitative variables will be compared between the two arms using a Chi-square test or Fisher's exact test, as appropriate. No intermediate analysis is planned.

Trends in arterial blood pressure and the group allocation will be assessed using a mixed regression model. If there is a significant interaction between groups or over time, post hoc analysis will be performed.

Data management and monitoring

Registration

Data are collected and registered using electronic case report forms (eCRFs) by a dedicated local research technician. A research coordinator centralises and verifies the data.

Record keeping

Consent forms and eCRFs will be retained for 15 years at the University Hospital of Amiens in accordance with French law.

Study organisation

The study is promoted by the University Hospital of Amiens, France. Amiens-Picardie University Hospital Clinical Research and Innovation Department help with the methodology, data management and biostatistics.

Duration and timeline

Patients from the Amiens University Hospital can be included for 3 years beginning from March 2022. The database should be closed after all participants have been included, followed by data analysis, writing of the manuscript and its submission for publication.

The investigator assesses each adverse event in terms of its seriousness. He notifies the sponsor of any serious adverse events or any new fact from the day he becomes aware of it without delay. All such events are followed up until their complete resolution.

Patient and public involvement

The patients were not involved in the recruitment or conduct of the study. The results of the study could be communicated to study participants on request. The burden of the intervention was not assessed by the patients themselves.

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Ethics and dissemination

The study was approved by the 'Comité de Protection des Personnes' IDF8 - Ile-de-France VIII (May 11, 2021, number 21 05 41 and the French Agency for the Safety of Medicines and Health Products (ANSM) (06/11/2021). The latest version (V3.1) was dated 11/06/2021.

The study is registered on the EudraCT database under N° EudraCT: 2021-001827-41. The study is registered on the ClinicalTrials.gov website with trial identification number NCT05276596. Oral information will be delivered, and written consent will be required before inclusion (extra online supplemental file 1).

The authors will be involved in disseminating the research findings (through attending conferences and co-authoring papers).

The results of the study will be disseminated via peer-reviewed publications and presentations at national and international conferences.

Trial status

Inclusion began on 3 March 2022.

As of 10 December 2023, 410 patients had been included in the study.

DISCUSSION

This is a prospective, randomised, single-centre, intention-to-treat, open-label, superiority study of two parallel groups assessing the value of the prophylactic use of norepinephrine during anaesthetic induction. Indeed, the incidence of IOH remains high in major abdominal surgery. There is strong evidence on the need to prevent IOH. Notably, the INPRESS[23] controlled trial confirmed that an individualised approach to blood pressure management is highly beneficial in terms of postoperative outcomes and mortality. This study led to the implementation of more appropriate therapeutic protocols, such as individualised blood pressure management, resulting in fewer adverse effects. There are many surgical causes of IOH, but anaesthesia is also a source of hypotension. We propose the prevention of arterial hypotension induced by anaesthetic induction.

This trial should provide strong results for an important clinical issue. Major abdominal surgery is common and the optimisation of arterial pressure during the induction period holds the potential to reduce postoperative death and complications. In addition, we plan a blinded assessment of the primary outcome to reduce detection bias. Data are routinely registered, and we expect little missing data. In addition, the periods of interest are all easily found in the patient file.

This is the first randomised controlled study to evaluate the preventive use of norepinephrine before anaesthetic induction in major abdominal surgery. The study's strength lies in its well-coded surgical complication score and homogeneous population. A limitation of our work is that we did not include an assessment of surgical satisfaction postoperatively, which could individually influence the Clavien–Dindo score. We hope to show that the prevention of hypotension induced by anaesthetic induction reduces postoperative medical and surgical complications.

Contributors OT-F: study design, manuscript draft and revision. CS, TF, MS, MR, RB and LV: co-investigators. SB: revision of the manuscript and co-investigator. JM is responsible for statistics and methodology and contributed to the study design. OA-A, SB and HD: manuscript revision. All authors approved the final version of the manuscript. All the authors of our work meet the four criteria recommended by the ICMJE. In fact, they participated in the design of the study or in the acquisition of the data, took part in the writing and validated the final manuscript. Each author accepts responsibility for this work.

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Competing interests None declared.

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

Patient consent for publication Not applicable.

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