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Early Use of Norepinephrine in High-risk Patients Undergoing Major Abdominal Surgery: A Randomized Controlled Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Hypotension after induction of anesthesia is common and may be associated with adverse outcomes; however, there is a lack of empirical data to characterize the impact of different vasopressor regimens on the risk of postoperative complications

What This Article Tells Us That Is New

- Compared to a strategy of ephedrine administration as needed to treat hypotension, continuous administration of norepinephrine infusion beginning at induction of anesthesia was associated with a lower rate of postoperative complications

ABSTRACT

Background: Intraoperative hypotension is a strong predictor of adverse outcomes in major abdominal surgery. However, data on the occurrence of intraoperative hypotension during the induction of general anesthesia are scarce. We hypothesized that early prevention of postinduction hypotension using a vasopressor could reduce postoperative adverse outcomes.

Methods: In this single-center randomized trial at Amiens Hospital University (Amiens, France), adults older than 50 yr with American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status II or greater undergoing major abdominal surgery were assigned to ephedrine or norepinephrine groups. In the ephedrine group, titration with iterative boluses of ephedrine (3 mg · ml^{-1}) was performed at the induction if intraoperative hypotension occurred. In the norepinephrine group, continuous intravenous injection of norepinephrine (0.016 mg · ml^{-1}) was started at a rate of 0.48 mg · h^{-1} from the induction of anesthesia and was titrated if intraoperative hypotension occurred. The primary endpoint was any medico-surgical complication within 30 days (Clavien–Dindo score of 1 or greater). Secondary endpoints included hospital stay length, acute kidney injury, 1-month mortality, and cardiovascular, respiratory, neurologic, and infectious complications. Results were assessed by blinded evaluators.

Results: A total of 500 patients were randomized, and 473 were included in the intention-to-treat analysis. The cumulative episodes of intraoperative hypotension were significantly lower in the norephedrine group in comparison to the ephedrine group (respectively, 35 [15%] *vs.* 176 [74%]; $P < 0.001$). The primary endpoint occurred in 137 patients (58%) in the ephedrine group and 103 patients (44%) in the norepinephrine group (relative risk, 0.58 [0.40 to 0.83]; $P = 0.004$). No significant differences were observed in secondary endpoints, except for pulmonary complications, which were lower in the norepinephrine group than in the ephedrine group (respectively; 40 [17%] *vs.* 74 [31%]; relative risk, 0.46 [0.29; 0.70]; $P < 0.001$).

Conclusions: Prophylactic titrated norepinephrine infusion to prevent postinduction hypotension was more effective than repeated ephedrine boluses and may reduce postoperative complications in major abdominal surgery.

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Abbreviations: **AKI**, acute kidney injury; **ASA**, American Society of Anesthesiologists; **EPON**, early use of norepinephrine; **MAP**, mean arterial pressure; **PACU**, postanesthesia care unit; **PPC**, postoperative pulmonary complication; **RR**, risk ratio

Intraoperative hypotension is a major concern in hemodynamics during major noncardiac surgery. Notably, the relationship between intraoperative hypotension and postoperative organ failure is no longer debated, as strong evidence demonstrates its association with an increased risk of myocardial injury, acute kidney injury (AKI), and mortality.[1–4] The longer and deeper the intraoperative hypotension, the greater the risk of adverse outcomes.

There is ongoing debate regarding the optimal mean arterial pressure (MAP) threshold to maintain, as large randomized trials have yielded conflicting results and failed to establish a definitive cutoff.[5–7] However, the latest guidelines recommend avoiding a MAP less than 60 to 65 mmHg in noncardiac surgery.[8–10]

Among the critical periods of intraoperative hypotension, the induction of general anesthesia is particularly significant.[11] Indeed, multiple factors contribute to a sudden shift in the patient's hemodynamic status when transitioning from wakefulness to unconsciousness, including a decrease in adrenergic stimulation, profound cardiovascular depression induced by anesthetic drugs, positive pressure ventilation, and patient frailty.[12–15] Therefore, the induction of general anesthesia is a critical period that often compromises hemodynamics leading to postinduction hypotension.

Vasopressors are the pharmacologic drugs that can prevent organ hypoperfusion. According to the recommendations of the French Society of Anesthesia and Intensive Care (Paris, France), ephedrine is the first-line treatment in the management of intraoperative. Its ß and α sympathomimetic effects promote an arterial vasoconstriction and a mild inotropic effect. Ephedrine is typically administered when intraoperative hypotension occurs; however, its main drawback is tachyphylaxis, which limits its duration of action. In recent years, norepinephrine has emerged as an alternative, supported by a growing body of literature, and is increasingly debated as a potential first-line vasopressor in anesthesia practice.[16,17] Notably, the prophylactic use of norepinephrine helps prevent intraoperative hypotension. One trial confirmed the safety of using norepinephrine at the induction of anesthesia, demonstrating a reduction in the incidence of intraoperative hypotension.[18]

To our knowledge, few large randomized trials have evaluated this strategy at the induction of general anesthesia. We hypothesized that the early use of norepinephrine to prevent postinduction hypotension could be beneficial in major abdominal surgery. Furthermore, our trial specifically targeted high-risk patients, based on their medical history, for whom intraoperative hypotension prevention is essential.

We conducted a large prospective single-center randomized trial to demonstrate that the early use of norepinephrine, compared to ephedrine, improves postoperative outcomes in high-risk patients undergoing major abdominal surgery. The primary outcome was the occurrence of medico-surgical complications within 30 days after surgery, defined by a Clavien–Dindo score of 1 or greater. Secondary outcomes included length of hospital stay, AKI, 1-month mortality, and cardiovascular, respiratory, neurologic, and infectious complications.

Materials and Methods

Ethics and Study Design

We conducted the Early Use of Norepinephrine (EPON) single-center, 1:1 ratio, open-label, prospective, randomized controlled trial at Amiens Hospital University (Amiens, France). This trial report followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines and checklist.[19] The study was approved by the "Comité de Protection des Personnes" Ile-de-France VIII (May 11, 2021; identifier No. 210541) and the French Agency for the Safety

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of Medicines and Health Products (Saint-Denis, France; June 11, 2021).[20] The study was registered on the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) database under No. 2021-001827-41 and on the ClinicalTrials.gov website with trial identification No. NCT05276596. Eligible patients were informed about the study and provided written informed consent during the preoperative anesthesia consultation, which took place within 30 days before surgery. Final eligibility was confirmed on the day of surgery, at which point patients were formally enrolled and randomized. The trial protocol and statistical analysis plan was previously described.[21]

Population Study

The population study was adult patients aged greater than 50 yr, with weight greater than 50 kg, with American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status score of II or greater, scheduled for a major abdominal surgery with general anesthesia.

The noninclusion criteria were emergency surgery, untreated or uncontrolled hypertension (systolic blood pressure greater than 150 mmHg), any acute cardiovascular event, including acute or decompensated heart failure or acute coronary syndrome, chronic kidney disease with a glomerular filtration rate of less than 30 ml · min^{-1}/1.73 m^2 or requiring renal replacement therapy for end-stage renal disease, severe hepatic failure (Alanine aminotransferase/Aspartate transaminase greater than 2 N, elevated bilirubin level, a prothrombin time less than 50%), preoperative sepsis, septic shock, preoperative norepinephrine infusion, patients eligible for a surgical procedure under locoregional anesthesia, pregnancy, known allergy to study treatment, and patients unable to give informed consent for any reason.

Intervention

In both groups, the aim of the intervention was to avoid a MAP under 65 mmHg or 70 mmHg in a patient with a medical history of hypertension (Supplemental Digital Content material S1, https://links.lww.com/ALN/E171).

In the norepinephrine group, continuous intravenous injection of norepinephrine (0.016 mg · ml^{-1}) was started before the induction of general anesthesia with a continuous infusion of 0.48 mg · h^{-1}. Titration was performed to achieve the previously defined target blood pressure values.

In the ephedrine group, intraoperative hypotension was managed with iterative boluses of ephedrine (3 mg · ml^{-1}) to a maximum dose of 30 mg. If the goal was not achieved, continuous intravenous injection of norepinephrine (0.016 mg · ml^{-1}) was started.

Standard Procedures and Definition of Intraoperative Hypotension

Anesthesia induction was proceeded with a combination of a hypnotic drug (etomidate or propofol), an opioid drug (sufentanil), and a curare (cisatracrium, atracurium, or rocuronium). The choice of hypnotic drug was at the discretion of the physician. The combination of a regional anesthesia (abdominal wall block or perimedullar anesthesia) was allowed. Blood pressure was monitored every 2 min. After induction, all patients were continuously monitored for stroke volume and arterial blood pressure using a radial artery line. Intraoperative fluid was managed with the administration of 250 ml lactated Ringer's solution when the change in stroke volume was greater than 15%, with an increase in stroke volume defining the responders. After orotracheal intubation, mechanical ventilation was started with a tidal volume of 8 ml · kg^{-1} ideal body weight, a positive end-expiratory pressure of 5 cm H_2O, a respiratory rate to obtain an end-tidal carbon dioxide between 35 and 40 mmHg, and an oxygen fraction to target oxygen saturation greater than 95%. The depth of anesthesia was monitored with a Bispectral Index (Medtronic, USA) target between 40 and 60. No preinduction fluid infusion was planned in the study. The induction period was defined as the time from the start of induction to the surgical incision.

Postinduction hypotension was defined as a MAP under 65 mmHg or under 70 mmHg in a patient with a medical history of hypertension.

An episode of MAP higher than 160 mmHg was considered as a hypertensive episode and declared as an adverse event and notified in the data collection.

Endpoints

The primary outcome was the occurrence of postoperative medico-surgical complications within 30 days after surgery. The primary endpoint was assessed using the Clavien–Dindo surgical score (Supplemental Digital Content file S2, https://links.lww.com/ALN/E171).[22] This score was 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). Postoperative complications were assessed by senior physicians (anesthesiologists, intensivists, and surgeons), as well as residents in anesthesiology. All were trained in the application of the Clavien–Dindo classification. Assessments were conducted based on predefined criteria and standardized procedures. When performed by residents, evaluations were systematically supervised and validated by a senior physician to ensure accuracy and consistency. Last, when a patient had several complications, only the more severe one was considered in the Clavien–Dindo scoring.

Secondary outcomes included length of hospital stay and length of intensive care unit/postoperative care unit stay; AKI at 48 h after surgery defined by an increase in creatinine greater than 26.5 μmol · l^{-1} from a reference value (preoperative value)[23]; and acute circulatory failure defined by the use of vasoactive drugs more than 12 h after.

The following complications were screened at 48 h, 7 days, and 1 month after surgery: cardiac complications (cardiac rhythm disorder, and/or acute coronary syndrome), postoperative pulmonary complications (PPC: pneumonia [presence of fever, respiratory symptoms, and a compatible radiological finding or microbiology], atelectasis [radiologically confirmed], oxygen support, mechanical ventilation or noninvasive ventilation, and/or acute respiratory distress syndrome[24]), infectious complications (sepsis defined as a Sequential Organ Failure Assessment of 2 points or more[25]), and neurologic complications (delirium, and/or stroke). At 1 month after surgery, the following endpoints were assessed: Instrumental activities of daily living (IADL scale)[26] and mortality.

Outcome data during hospitalization were collected through direct assessment by the clinical research team. At 1-month follow-up, data were obtained through electronic medical record review and a routine postoperative surgical visit. In addition, all patients were contacted by telephone at 1 month to confirm the presence or absence of complications.

Randomization and Blinding

Patients were randomized into two parallel open-label groups using computer-generated block randomization (Ennov Clinical software, Ennov, Paris, France), with fixed-size random blocks and stratification based on the anesthetic induction drug (etomidate or propofol). Group allocation was labeled as "ephedrine group" or "norepinephrine group." As this was an open-label trial, both the anesthesiologists and the patients were aware of group assignment during induction. However, the evaluation of outcomes—including the primary endpoint and postoperative complications—was performed by clinical staff who were not involved in anesthesia care and were blinded to treatment allocation. This blinding was maintained during the entire postoperative hospitalization and at the 1-month follow-up.

Sample Size Calculation

The medico-surgical complication rate found in the literature is between 25 and 30%.[27] Thus, we set the rate of medical and surgical complications (defined by a Clavien–Dindo score of 1 or greater) to 25% in the control group, the inclusion of 500 patients (250 in each arm) to an absolute difference of 10% between groups, with an alpha risk of 5% and a power of 80%, and an expected loss to follow-up of 5%.

Statistical Analysis

Data were expressed as median [interquartile range], mean ± SD, or number (percentage), as appropriate. The primary outcome was reported as "intention to treat." The primary endpoint was assessed using a binomial generalized linear mixed model with a fixed effect for the group. Secondary endpoints were assessed using a binomial generalized linear mixed model or a linear generalized linear mixed model. We reported the risk ratio (RR) and its 95% CI for the primary endpoints and the secondary categorial endpoints. We reported the absolute difference of endpoints as the difference in ephedrine minus norepinephrine group and its 95% CI. No intermediate analysis was planned.

Repeated measures of MAP and stroke volume were compared between groups using a linear mixed model including arm as a fixed effect.

Quantitative variables were compared between groups 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 exact test, as appropriate. Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria), Version 2025.05.0+496 https://www.r-project.org/.

Results

Participants

Between November 17, 2021, and April 3, 2024, a total of 1,260 patients were assessed for eligibility, and 500 patients scheduled for major abdominal surgery were included in the EPON study (fig. 1). These 500 patients were randomized into two identical groups. The ephedrine group included 252 patients, and the norepinephrine group included 248 patients. Among them, three patients withdrew their consent after randomization: one in the ephedrine group and two in the norepinephrine group. In the ephedrine group, 13 patients were retrospectively excluded (8 patients were classified as "not undergo surgery" because the planned surgical procedure was ultimately not performed, and in 5 cases, patients were excluded from the analysis because no data were available, owing to a protocol violation; fig. 1). Finally, 235 and 238 patients were analyzed, respectively, for the ephedrine and the norepinephrine groups.

Patients were at the median age of 68 yr in both groups and mainly represented by men. In both groups, ASA Physical Status III prevailed. All patients had a medical history mainly represented by a cancer followed by hypertension. Most patients underwent for digestive surgery (more than a half), followed by urologic and gynecological surgeries (table 1).

Intraoperative Characteristics

During the induction period, a significantly lower proportion of patients in the norepinephrine group experienced one or more episodes of intraoperative hypotension compared to the ephedrine group (35 patients [15%] *vs.* 176 patients [74%], respectively; $P < 0.001$). MAP did not significantly differ at baseline between groups. After induction, MAP was significantly higher at 5, 10, and 30 min after induction in the norepinephrine group compared to the ephedrine group (between-groups $P < 0.001$; table 2; fig. 2; Supplemental Digital Content figures 1 and 2, https://links.lww.com/ALN/E171). MAP significantly differed at

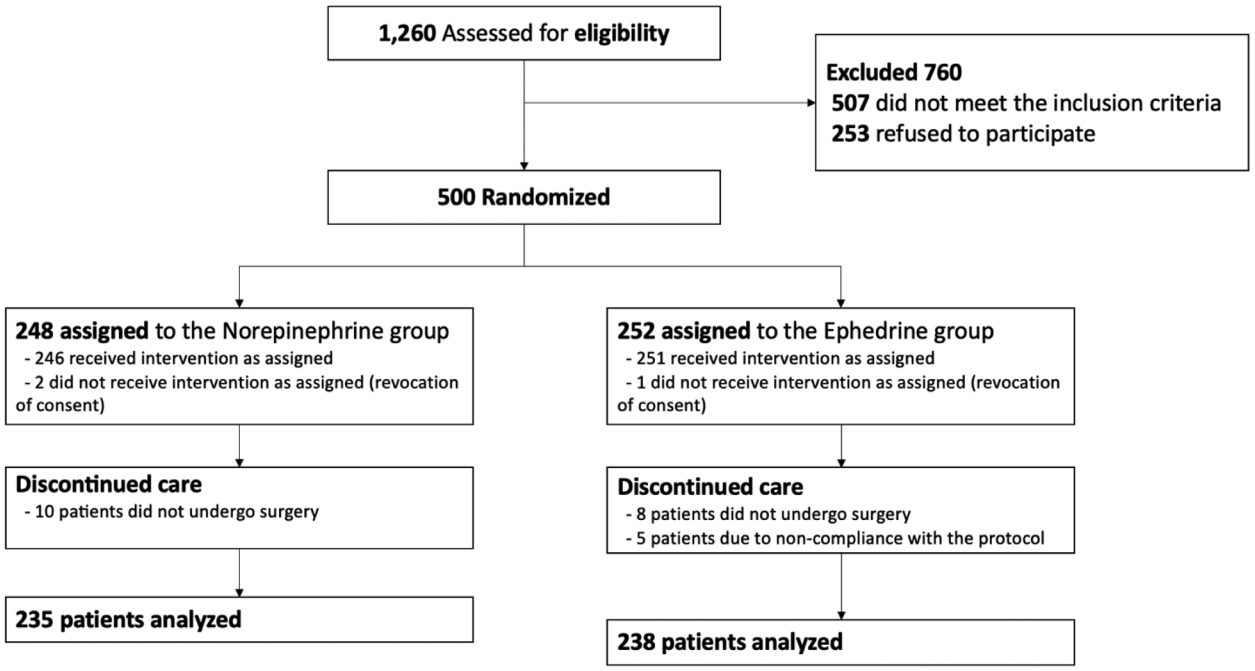

Fig. 1. Flow chart.

each timepoint measurement between the ephedrine and the norepinephrine groups. Respectively at 5 min, MAP was at 68 [59 to 82] and 86 [74 to 97] mmHg ($P < 0.001$). Respectively at 10 min, MAP was at 69 [61 to 80] and 77 [69 to 88] mmHg ($P < 0.001$). Respectively at 30 min, MAP was at 73 [65 to 83] and 76 [69 to 86] mmHg ($P = 0.012$)

In the ephedrine group, the cumulative dose of ephedrine during the postinduction period was 0.38 [0.38–0.38] mg/kg. When considering the entire intraoperative period, the total cumulative norepinephrine dose was significantly higher in the norepinephrine group compared to the ephedrine group (0.80 [0.52 to 1.12] *vs.* 0.54 [0.36 to 0.79] μg/kg; $P < 0.001$; table 2).

Arterial lactate was significantly lower in the norepinephrine group compared to the ephedrine group during the intraoperative time (respectively, 1.5 [1.2 to 2.1] *vs.* 1.7 [1.4 to 2.2] mmol l^{-1}; $P = 0.033$) and at postanesthesia care unit (PACU) admission (respectively, 2.0 [1.3 to 3.2] *vs.* 2.4 [1.7 to 3.7] mmol l^{-1}; $P < 0.001$).

Other biologic investigations regarding creatinine, troponin, hemoglobin or Pao_2 did not show any significant difference during the intraoperative time or at PACU admission.

The type of hypnotic induction drug and the duration of surgery did not significantly differ between groups.

Main Endpoint

The primary endpoint occurred in 137 patients (58%) in the ephedrine group and in 103 patients (44%) in the norepinephrine group (risk ratio at 0.58 with a 95% CI at 0.40 to 0.83; $P = 0.004$; table 3).

Patients significantly differed for grade I and grade II of the Clavien–Dindo score, with a lower rate in the norepinephrine group (grade I: 23% *vs.* 16%; RR, 0.52 [0.31–0.84]; $P = 0.008$; grade II: 17% *vs.* 11%; RR, 0.52 [0.30–0.90]; $P = 0.019$; Supplemental Digital Content Table S3, https://links.lww.com/ALN/E171).

Grades III, IV, and V were similar between groups (grade IIIA: 5% *vs.* 4%; RR, 0.63 [0.24 to 1.59]; $P = 0.327$; grade IIIB: 1% *vs.* 0%; RR, 0.60 [0.30 to 1.17]; $P = 0.136$; grade IVA: 2% *vs.* 3%; RR, 1.06 [0.32 to 3.79]; $P = 0.922$; grade IVB: 1% *vs.* 0%; RR, 0.41 [0.01 to 5.11]; $P = 0.487$; and grade V: 0% *vs.* 2%; RR, 2.77 [0.38 to 76.4]; $P = 0.346$; Supplemental Digital Content Table S3, https://links.lww.com/ALN/E171).

Secondary Endpoints

There was no significant difference in hospital length of stay between the two groups (respectively for the ephedrine and the norepinephrine groups: 7 [5 to 11] and 6 days [4 to 11]; absolute difference, 1 [−2 to 0]; $P = 0.321$).

PPC at 48 h occurred in 40 patients (17%) in the norepinephrine group and in 74 patients (31%) in the ephedrine group (risk ratio at 0.46 with a 95% CI at 0.29 to 0.70; $P < 0.001$). PPC at 7 days and 1 month did not significantly differ between groups (table 3).

Neurologic, infectious, and cardiovascular complications did not significantly differ between groups. Details of complications are presented in Supplemental Digital Content material S3 (https://links.lww.com/ALN/E171).

Table 1. Demographic Characteristics and Surgery Type

Variables	Ephedrine Group (n = 238)	Norepinephrine Group (n = 235)
Age, yr	68 [61–73]	68 [61–74]
BMI, kg · m^{-2}	27.0 [24.1–30.4]	26.1 [23.2–30.0]
Male gender type, n (%)	163 (68)	154 (66)
ASA Physical Status, n (%)		
II	89 (37)	104 (44)
III	149 (63)	131 (56)
Medical history, n (%)		
Arterial hypertension	129 (54)	120 (51)
Coronary disease	24 (11)	22 (10)
Chronic heart failure	4 (2)	4 (2)
Chronic kidney disease	29 (12)	33 (14)
Cirrhosis	18 (8)	7 (3)
COPD	22 (9)	4 (10)
Active cancer	218 (92)	201 (86)
Surgery type, n (%)		
Digestive	154 (65)	135 (57)
Urologic	74 (31)	91 (39)
Gynecological	10 (4)	9 (4)
Biologic investigations		
Hemoglobin, g · dl^{-1}	13.2 ± 1.9	13.3 ± 1.8
eGFR, ml · min^{-1}	86 [70–103]	84 [67–103]

ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, glomerular filtration rate.

The mortality rate at 1 month did not differ between the ephedrine and the norepinephrine group (respectively at 1 [0%] and 4 [1%]; relative risk at 0.27 with a 95% CI, 0.01 to 1.96; $P = 0.212$).

Subgroup Analysis

Subgroup analysis was performed to assess the influence of patients' medical history, ASA Physical Status, and type of surgery on the primary outcome. The treatment effect was significantly more beneficent for patients with ASA Physical Status III (RR, 0.60 [0.36 to 0.99]; $P = 0.048$), without chronic kidney disease (RR, 0.63 [0.42 to 0.94]; $P = 0.025$), without chronic obstructive pulmonary disease (RR, 0.57 [0.38 to 0.85]; $P = 0.006$), male patients (RR, 0.53 [0.33 to 0.84]; $P = 0.008$), and those undergoing digestive surgery (RR, 0.61 [0.37 to 0.99]; $P = 0.046$). No significant differences were found in the other subgroups (fig. 3).

Discussion

In this trial, we observed a significant reduction in the risk of medical–surgical complications (Clavien–Dindo score of 1 or greater) at 30 days after major abdominal surgery with a strategy of postinduction hypotension prevention using

Table 2. Intraoperative Characteristics between Groups

Variables	Ephedrine (n = 238)	Norepinephrine (n = 235)	Absolute Difference (95% CI)	*P* Value
Patients with at least 1 intraoperative hypotension episode, n (%)	176 (74)	35 (15)	59 (51 to 66)	< 0.001*
Cumulative duration of intraoperative hypotension, min	10 [10 to 20]	10 [5 to 10]	5 (2 to 7)	< 0.001*
Hypertension episodes, n (%)	0 (0)	42 (18)	—	—
MAP, mmHg				
Baseline	101 ± 13	102 ± 13	–1 (–3 to –2)	0.484
Induction + 5 min	68 [59 to 82]	86 [74 to 97]	–14 (–18 to –11)	< 0.001*
Induction + 10 min	69 [61 to 80]	77 [69 to 88]	–8 (–11 to –5)	< 0.001*
Induction + 30 min	73 [65 to 83]	76 [69 to 86]	–3 (–5 to –0)	0.012*
Surgery duration, min	258 [195 to 333]	248 [201 to 331]	10 (–14 to 21)	0.801
Hypnotic induction drug, n (%)				
Etomidate	8 (3)	15 (6)		0.192
Propofol	229 (97)	220 (94)		
Cumulative fluid volume, ml	3,000 [2,000 to 4,000]	3,000 [2,500 to 4,000]	–194 (–481 to 93)	0.510
Blood loss, ml	300 [100 to 550]	250 [100 to 600]	19 (–95 to 57)	0.908
Cumulative diuresis, ml · kg^{-1} · h^{-1}	1.4 [0.9 to 2.2]	1.5 [1.0 to 2.3]	–0.1 (–0.3 to 0.1)	0.334
Cumulative ephedrine dose, mg · kg^{-1}	0.38 [0.38 to 0.38]	—	—	—
Cumulative NE dose during the whole surgery, µg · kg^{-1}	0.54 [0.36 to 0.79]	0.8 [0.52 to 1.12]	–0.26 (–0.33 to –0.16)	< 0.001*
Intraoperative biologic investigations				
Arterial lactate, mmol · l^{-1}	1.7 [1.4 to 2.2]	1.5 [1.2 to 2.1]	0.4 (0.0 to 0.7)	0.033*
Creatinine, µmol · l^{-1}	66 [54 to 86]	64 [53 to 81]	2 (–7 to 3)	0.705
Hemoglobin, g · dl^{-1}	12.3 ± 1.8	12.0 ± 1.8	–0.2 (–0.1 to 0.6)	0.202
$Pa0_2$, mmHg	146 [118 to 180]	156 [126 to 188]	–6 (–15 to 3)	0.104
Troponin, ng · ml^{-1}	4 [3 to 9]	4 [2 to 7]	–1 (–6 to 8)	0.288

Data were expressed as mean ± SD or as median [interquartile range] or as number (percentage) as appropriate. Cumulative duration of intraoperative hypotension concerns only patients with a MAP under 65 mmHg. Patients with no intraoperative hypotension were not considered in the calculation. The absolute difference reflects ephedrine minus norepinephrine difference. Data were compared using a *t* test, a Wilcoxon–Mann–Whitney test, and a chi-square test depending on the variable type. A *P* value < 0.05 was considered as significant for a statistical test.

*$P < 0.05$.

MAP, mean arterial pressure; NE, norepinephrine.

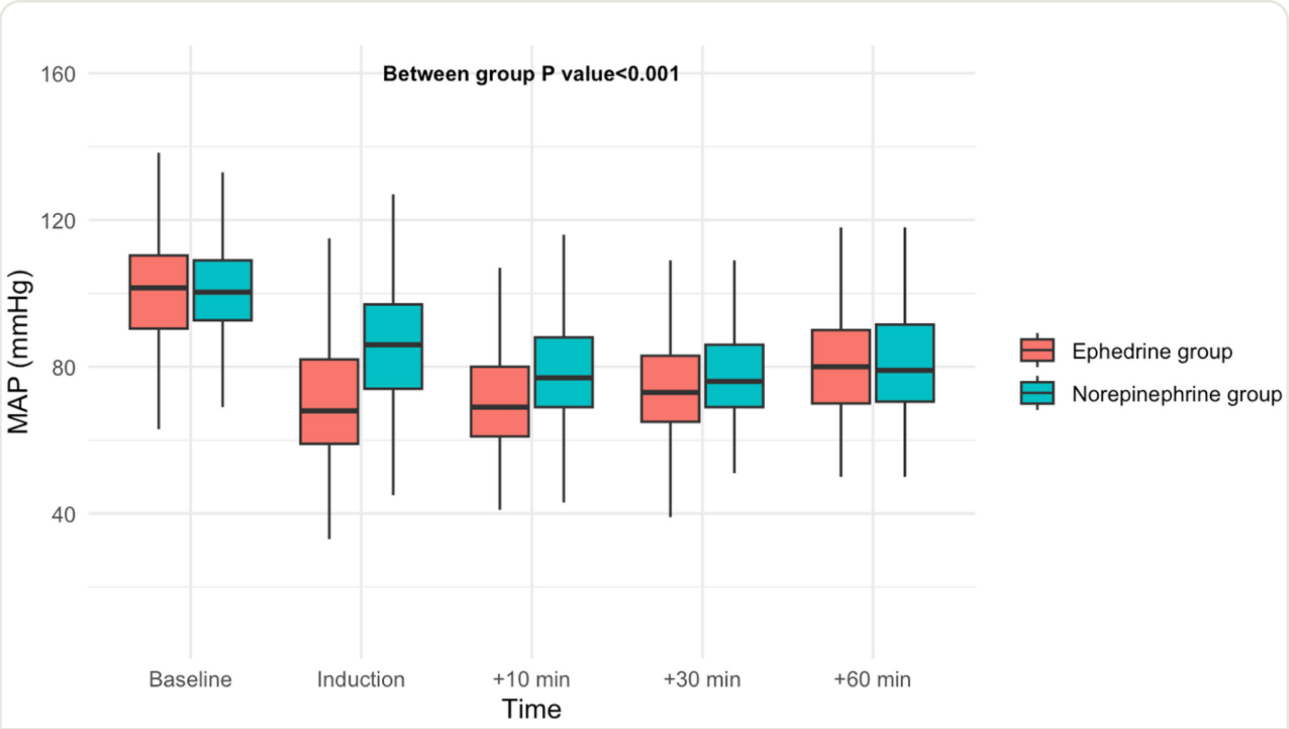

Fig. 2. Mean arterial pressure (MAP) comparison between groups from baseline to 60 min after induction. *Box plots* represent the median with the interquartile range.

norepinephrine, compared to the standard care strategy using curative ephedrine. Regarding secondary endpoints, we observed a significant decrease in PPC at 48 h; however, this difference was not sustained at 7 days or 1 month. Last, no meaningful differences were observed in neurologic, infectious, or cardiovascular complications.

Risk factors of postinduction hypotension in general anesthesia are well documented.[11] We confirmed the findings of a previous feasibility trial in which the authors demonstrated that norepinephrine effectively prevents postinduction hypotension in a pilot study.[18] Beyond that, we could demonstrate that postinduction hypotension prevention allows a reduction risk in medico-surgical complications in major abdominal surgery. In our trial, the risk reduction primarily affected Clavien–Dindo grade I and II complications, which correspond mainly to nonsurgical complications. The intervention significantly decreased postinduction hypotension, accompanied by a concomitant reduction in lactate levels during surgery and upon PACU admission (table 2). However, we observed a higher incidence of hypertensive episodes, although biologic investigations showed no evidence of myocardial or kidney injury (table 2).

Regarding complications, we noted a reduction in postoperative complications, primarily characterized by a decreased need for oxygen therapy. This finding aligns with existing literature, which suggests that goal-directed hemodynamic therapy contributes to a reduction in pulmonary complications.[28] That finding may be surprising given the lack of a consistent mechanistic explanation linking the prevention of hypotension to improvements in pulmonary outcomes. Goal-directed therapies are generally expected to improve pulmonary outcomes by optimizing intravenous fluid administration. A meta-analysis confirmed that in patients undergoing major abdominal surgery, goal-directed therapy improves pulmonary outcomes, including reducing acute respiratory distress syndrome and pneumonia.[28] However, no differences in fluid management were observed between groups in our study. We must acknowledge that the rationale behind our findings is not robust and warrants further investigation to elucidate the underlying mechanisms. Overall, these findings should be interpreted with caution, especially considering the limitations of our study.

However, our study presents a novel approach to managing postinduction hypotension, a challenging phase of anesthesia, particularly in high-risk patients. It demonstrates that proactive management during the postinduction period is feasible, as evidenced by a lower incidence of hypotension, and may provide significant benefits for patients.

Our study also provides insights into which hemodynamic parameters should be optimized during this challenging period. While we targeted MAP in our trial, previous large studies have focused on stroke volume, based on the rationale that stroke volume should be maintained, potentially through the use of inotropic agents when necessary.[29,30] However, it

Table 3. Primary and Secondary Outcomes

Variables	Ephedrine Group (n = 238)	Norepinephrine Group (n = 235)	Absolute Difference (95% CI)	Risk Ratio (95% CI)	*P* Value
Primary outcome					
Clavien–Dindo ≥ 1, n (%)	137 (58)	103 (44)	14 (3 to 22)	0.58 (0.40 to 0.83)	0.004*
Secondary outcomes					
ICU stay, days	2 [1 to 4]	2 [1 to 3]	1 (–2 to 0)		0.478
Hospital length of stay, days	7 [5 to 11]	6 [4 to 11]	0 (–2 to 2)		0.321
AKI at 48 h, n (%)	20 (12)	27 (18)	–4 (–2 to 6)	1.58 (0.85 to 3.00)	0.195
Acute circulatory failure at 48 h, n (%)	4 (2)	11 (5)	–3 (–5 to 9)	2.80 (0.93 to 10.5)	0.069
CV complication, n (%)					
48 h	8 (3)	11 (5)	–2 (–4 to 2)	1.40 (0.55 to 3.74)	0.478
7 days	10 (4)	8 (3)	0 (–3 to 4)	0.81 (0.30 to 2.11)	0.661
1 month	6 (3)	13 (6)	–3 (–6 to 5)	2.23 (0.86 to 6.56)	0.102
PPC, n (%)					
48 h	74 (31)	40 (17)	14 (6 to 22)	0.46 (0.29 to 0.70)	< 0.001*
7 days	34 (14)	22 (9)	5 (–1 to 10)	0.62 (0.35 to 1.09)	0.130
1 month	12 (5)	19 (8)	–3 (–8 to 2)	1.65 (0.79 to 3.59)	0.188
Infectious complications, n (%)					
48 h	26 (11)	16 (7)	4 (–1 to 9)	0.60 (0.31 to 1.14)	0.119
7 days	34 (14)	30 (13)	–2 (–5 to 8)	0.88 (0.52 to 1.49)	0.632
1 month	12 (5)	19 (8)	–1 (–6 to 7)	1.65 (0.79 to 3.59)	0.188
Neurologic complications, n (%)					
48 h	1 (0)	3 (1)	–1 (–3 to 1)	2.81 (0.32 to 81.0)	0.367
7 days	1 (0)	0 (0)	—	—	1.000
1 month	5 (2)	7 (3)	0 (–4 to 2)	1.42 (0.44 to 4.99)	0.562
IADL scale at 1 month	6 [6 to 6]	6 [6 to 6]	0 (–1 to 1)	—	0.234
Mortality at 1 month, n (%)	1 (0)	4 (1)	–1 (–5 to 3)	0.27 (0.01 to 1.96)	0.212

The primary endpoint was assessed within 30 days after the surgery. The absolute difference reflects ephedrine minus norepinephrine difference.

*$P < 0.05$.

AKI, acute kidney injury; CV, cardiovascular; IADL, Instrumental activities of daily living; ICU, intensive care unit; PPC, postoperative pulmonary complication.

appears that the use of inotrope does not provide any relevant clinical benefit for the patients. Moreover, in one trial, the use of inotrope drug led to more cardiac adverse events related to the dobutamine side effects.[30] In our trial, data from some patients revealed that stroke volume variation was not a major issue, whereas mean arterial pressure variation was more relevant. We believe that further investigations should probably focus on MAP rather than on stroke volume, although the stroke volume deserves a strict monitoring in some elected patients (known severe heart failure or heart disease).

Our trial addresses another key concern: the optimal choice of vasopressor in major noncardiac surgery.[9] Norepinephrine is an α1- and β1-adrenergic agonist that maintains MAP and cardiac output, although we did not observe an increase in stroke volume in our study. Conversely, excessive exposure to norepinephrine could compromise organ perfusion, potentially leading to organ injury. This concern requires caution, as it has been highlighted in retrospective studies on both noncardiac and cardiac surgeries.[31,32] However, we did not confirm this finding in our study. Hence, there is ongoing debate about both the optimal MAP threshold to maintain during anesthesia and the most appropriate choice of vasopressor. Two large randomized trials have addressed these specific questions, which remain unresolved to date. The PeriOperative Ischemic Evaluation Study (POISE) group investigated two MAP targets in patients receiving chronic antihypertensive medication.[6] They found no significant difference in the incidence of major cardiovascular events among more than 7,000 patients. Additionally, Legrand *et al.* compared phenylephrine and norepinephrine in more than 3,000 patients undergoing noncardiac surgery.[17] This study was a feasibility trial conducted in preparation for a larger multicenter study. Both vasopressors demonstrated similar outcomes regarding hospital readmission, 30-day mortality, and myocardial injury. It is important to highlight that these studies assessed the entire perioperative period, whereas our focus was specifically on the challenging postinduction phase.

Our trial had limitations. Notably, in recent years, many goal-directed hemodynamic therapies have failed to demonstrate a clinical benefit. Indeed, it has been highlighted that positive findings from small-sample trials are often inconclusive when tested in large, multicenter randomized trials.[30,33] The authors conducted a well-designed meta-analysis demonstrating that the treatment effect was significantly influenced by the trial size.[33] The larger the trial size, the more likely it is to yield negative results. This raises the question of whether our single-center trial, with a sample size of 500 patients, may have overestimated the treatment effect and whether the findings would be confirmed in a larger, multicenter randomized trial.

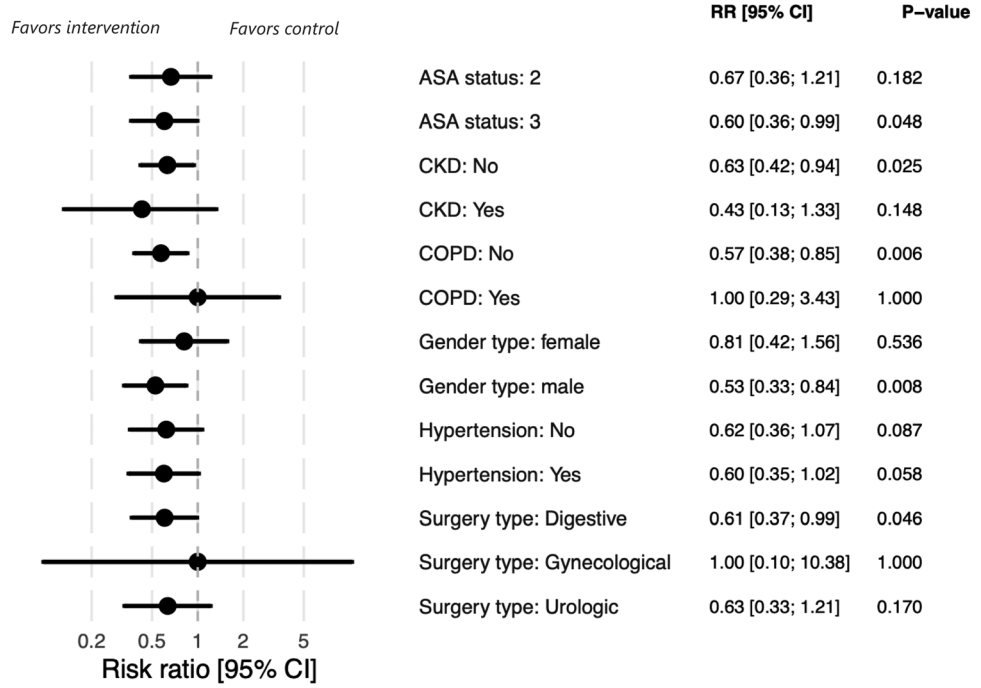

Fig. 3. Primary outcome according to subgroup. A risk ratio (RR) and its 95% CI are represented for each subgroup. ASA, American Society of Anesthesiologists; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Another limitation is the higher-than-expected complication rate.[21] Based on a seminal study linking surgical complexity to Clavien–Dindo grades and assuming a balanced mix of moderate- to high-complexity procedures, we estimated a 25 to 30% rate.[22] However, our population was mostly composed of highly complex surgeries, which likely explains the higher observed rate. In addition, our cohort included high-risk surgical patients, whose comorbidities inherently increased the risk of complications. Moreover, the single-center design of our study might explain that discrepancy. This highlights the inherent limitation of a single-center design and the need for external validation to confirm the generalizability of our findings. Despite a higher overall rate, our findings align with previous data, with close rates in colorectal surgery (58%) and even higher in pancreatic surgery (64%).[34–36] Last, when comparing our findings to more recent trials on major abdominal surgery, the incidence of complications (such as AKI, pneumonia, and mortality) falls within a similar range.[29,30]

Actually, the intervention tested in our trial included multiple components: different vasopressor agents (norepinephrine *vs*. ephedrine), the timing of administration (preemptive *vs*. reactive to hypotension), and the mode of administration (continuous infusion *vs*. bolus). Indeed, we compared two vasopressors in two different modes administration. Hence, we cannot distinguish which of the administration type (bolus or continuous infusion) or the vasopressor type was the more beneficial for the patient. However, a very recent study from Thomsen *et al*. compared bolus to continuous bolus of norepinephrine in a surgical population in a randomized clinical trial.[37] They reported an absence of benefit of one strategy over the other to treat postinduction hypotension. That finding provides a partial response and suggests that the issue may relate more to the type of vasopressor than to the mode of administration.

Conversely, the treatment effect aligned with our expectations. In the protocol, we anticipated a 10% treatment effect, while our final report showed a 14% effect (table 3).[21]

One of the strengths of our study is its specific focus on the intraoperative hypotension after the induction of general anesthesia. To our knowledge, this is the first trial to address that challenging period of anesthesia. Major previous randomized trials focused on the overall surgical time.[6,7,17]

Among perspectives, we believe our findings provide rationale for the further use of a closed loop of norepinephrine, which may prevent intraoperative hypotension and improves outcomes, as reported previously.[38]

Conclusions

Prophylactic titrated norepinephrine infusion to prevent postinduction hypotension was more effective than

repeated ephedrine boluses and may reduce postoperative complications in major abdominal surgery.

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Competing Interests

Dr. Abou-Arab reports personal fees from Edwards Lifesciences (Irvine, California) outside the submitted work. The others authors declare to no competing interests.

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Supplemental Digital Content

Supplemental materials, figures, and tables, https://links.lww.com/ALN/E171

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