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Journal

Journal of clinical monitoring, 38(1)

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Publication Date

2024-02-01

DOI

10.1007/s10877-023-01104-3

Peer reviewed

HHS Public Access

Author manuscript

J Clin Monit Comput. Author manuscript; available in PMC 2024 August 14.

Published in final edited form as:

J Clin Monit Comput. 2024 February ; 38(1): 19–24. doi:10.1007/s10877-023-01104-3.

Tight control of mean arterial pressure using a closed loop system for norepinephrine infusion after high-risk abdominal surgery: a randomized controlled trial

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Abstract

Intensive care unit (ICU) nurses frequently manually titrate norepinephrine to maintain a predefined mean arterial pressure (MAP) target after high-risk surgery. However, achieving this task is often suboptimal. We have developed a closed-loop vasopressor (CLV) controller to better maintain MAP within a narrow range. After ethical committee approval, fifty-three patients admitted to the ICU following high-risk abdominal surgery were randomized to CLV or manual norepinephrine titration. In both groups, the aim was to maintain MAP in the predefined target of 80–90 mmHg. Fluid administration was standardized in the two groups using an advanced hemodynamic monitoring device. The primary outcome of our study was the percentage of time patients were in the MAP target. Over the 2-hour study period, the percentage of time with MAP in target was greater in the CLV group than in the control group (median: $IQR_{25–75}$: 80 [68–88]% vs. 42 [22–65]%), difference 37.2, 95% CI (23.0–49.2); $p < 0.001$). Percentage time

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Author contributions SC: analyzed data and wrote the manuscript. MSP: collected data and revised the manuscript. PVdL: analyzed data, prepared the figures, and revised the manuscript. MCl: analyzed data and revised the manuscript. JR: analyzed data and revised the manuscript. MC: analyzed data and revised the manuscript. JD: analyzed data and revised the manuscript. AJ: recruited patients, analyzed data, and reviewed the manuscript.

Conflict of interest Alexandre Joosten, Maxime Cannesson, and Joseph Rinehart are consultants for Edwards Lifesciences, USA. They have ownership interest in Sironis, and Sironis has developed the closed-loop vasopressor system used in this study. Sironis provided no direct or indirect funding in support of the current work, to the individual authors, or any of their respective departments. The other authors have no conflicts of interest concerning this study.

Ethical approval This study was approved on August 24th, 2020, by the Comité de Protection des Personnes Sud-Est I (2020-A01149-30) and registered prior to patient enrollment on clinicaltrials.gov (NCT04639037: November 20th, 2020).

with MAP under 80 mmHg (1 [0–5]% vs. 26 [16–75]%, p < 0.001) and MAP under 65 mmHg (0 [0–0]% vs. 0 [0–4]%, p = 0.017) were both lower in the CLV group than in the control group. The percentage of time with a MAP > 90 mmHg was not statistically different between groups. In patients admitted to the ICU after high-risk abdominal surgery, closed-loop control of norepinephrine infusion better maintained a MAP target of 80 to 90 mmHg and significantly decreased postoperative hypotensive when compared to manual norepinephrine titration.

Keywords

Hypertension; Hypotension; Intraoperative monitoring; Safety; Vasopressor agents; Automation

1 Introduction

Vasopressor infusions, which are often manually titrated by intensive care unit (ICU) nurses, are an essential component of postoperative hypotension treatment. While optimal blood pressure targets remain uncertain, the available studies are limited by difficulty in maintaining targets within the desired range [1, 2]. Nonetheless, both over- and under- treatment increase the risk of renal and cardiac complications. Tight and accurate vasopressor titration are of major importance in high-risk surgical patients, but nurses can find this difficult to achieve in an often overworked ICU environment.

We developed a closed-loop vasopressor (CLV) controller to better control perioperative hypotension and showed that this system outperformed manual titration of vasopressors during high-risk surgery and after cardiac surgery. [3-5] We tested the hypothesis that the CLV would also better maintain MAP within a target (defined as a MAP between 80 and 90 mmHg) when compared to standard norepinephrine management in patients admitted to the ICU after high-risk abdominal surgery.

2 Materials and methods

This bi-center, randomized controlled superiority study was approved on August 24th, 2020, by the Comité de Protection des Personnes Sud-Est I (2020-A01149-30) and registered prior to patient enrollment on clinicaltrials.gov (NCT04639037: November 20th, 2020). Patients gave written informed consent to participate before surgery.

2.1 Patient inclusion and non-inclusion criteria

All adult French speaking patients who underwent liver transplantation, Whipple procedure, major liver resection, or total cystectomy at the Paul-Brousse and the Kremlin-Bicêtre hospitals were considered for inclusion. Children and patients refusing to participate or unable to give consent (e.g., already under mechanical ventilation or language barrier) were not included. All included patients gave written informed consent.

2.2 Randomization and blinding

A randomization sequence was generated using the internet-based program http://randomization.com. Group allocation was concealed in sealed opaque envelopes and a study

nurse not associated with patient care allocated patients to their randomized group before surgery. Patients, clinicians carrying for the patient intraoperatively, and the investigator collecting data were blinded to group allocation. A single investigator was present in the ICU during the study protocol for the CLV patients to ensure the proper use of the system.

2.3 Closed-loop vasopressor controller

The CLV has been previously described [6-8]. Briefly, this system uses predictive and rules-based control modules to administer norepinephrine and maintain MAP within a predefined target. The algorithm is coded in Microsoft Visual C (Microsoft Corp, Redmond, WA). Version 2.93 of the CLV controller software was used for all the patients in this study. The controller software was run on an Acer laptop using Windows 7 (Microsoft Corp, Redmond, CA). It was connected to a serial output on an EV-1000 monitor and a Chemyx Fusion 100 syringe pump (Chemyx Inc, Stafford, TX, United States).

2.4 Anesthesia protocol

All patients were monitored with pulse oximetry, non-invasive blood pressure, 3 or 5 lead EKG, inhaled and expired gases, rectal temperature probe and invasive blood pressure measurement through radial, femoral, or brachial artery catheterization. Frontal electroencephalogram monitoring with the Bispectral index, hemodynamic pulse-contour analysis, central venous pressure, and other supplemental monitoring tools (i.e. pulmonary artery catheter in case of liver transplantation) were used at the discretion of the attending anesthetist.

Anesthesia was induced with propofol or etomidate, and sufentanil. Neuromuscular blockade was obtained with succinylcholine, rocuronium, or atracurium. Anesthesia was maintained with sevoflurane. Adjuvant antinociception with locoregional local anesthetics and opioid sparing agents were administered at the discretion of the attending anesthetist.

The vasopressor of choice was norepinephrine, although both phenylephrine and ephedrine were also used before establishment of a central venous access. Intraoperative hypotension, defined as a MAP below 65 mmHg was treated with manual titration of vasopressors. Boluses of Ringer's lactate or 5% albumin were titrated to avoid preload dependence by maintaining stroke volume variation under 13%.

2.5 Postoperative period and study protocol

All patients were admitted postoperatively in the ICU. They were mechanically ventilated and sedated with propofol and sufentanil. Fluid administration was standardized in the two groups using an advanced hemodynamic monitoring device: fluid challenges were administered using the EV-1000 (Edwards Lifesciences, Irvine, CA, USA) clinical platform to optimize stroke volume index. Fifteen minutes after their admission, patient group allocation was revealed and the 2-h study period began. The MAP target was set between 80 and 90 mmHg through norepinephrine infusion (32 μg/ml). In the control group, norepinephrine was titrated manually by the ICU nurse to maintain MAP within a target range of 80–90 mmHg. In the CLV group, norepinephrine was automatically delivered by the closed-loop system to maintain MAP within the same target range.

2.6 Study measurements and outcomes

The primary outcome of the study was the percentage of the study period (i.e., the first two postoperative hours in the ICU) during which MAP was “in target” (between 80 and 90 mmHg). During the study protocol, data were collected by the closed-loop system every 2 s. Data collection included timestamp, MAP, infusion rate of norepinephrine, and multiple other parameters related to the closed-loop operation. Because the control group did not have the closed-loop intervention, but both groups had EV-1000 monitoring, the EV-1000 MAP data (sampled once every 20 s) was used for analysis of blood pressures and time-in-target comparisons. Secondary outcomes included the incidence of hypotension (defined as MAP < 80 and MAP < 65 mmHg); incidence of hypertension (defined as MAP > 90 mmHg); fluid and norepinephrine volumes received during the study period, and ICU and hospital lengths of stay. Hemodynamic variables (MAP, heart rate, stroke volume index, cardiac index) were recorded every 20 s with the EV-1000 monitor and subsequently averaged.

2.7 Statistical analysis

Local data obtained retrospectively showed that patients spent 50% of the time with a MAP of 85 ± 5 mmHg when norepinephrine was manually titrated versus 85% of the time when administered with the CLV [1]. Therefore, we estimate that to have a power of 80% to demonstrate a difference of 50% versus 85% on the primary endpoint (absolute change) between groups, 27 patients per group would be needed. We therefore planned to include up to 35 patients per group, to consider possible drop out.

Quantitative variables are described as mean with standard deviation or median with [25–75] percentiles and were analyzed using Student’s or Mann–Whitney’s t-test depending on the distribution of the data (assessed using the Kolmogorov–Smirnov test). Qualitative variables were measured as counts and proportions and analyzed using a Chi-square test or Fisher's exact probability test. A value of $p < 0.05$ was considered statistically significant. All data were analyzed using an intention-to-treat approach.

3 Results

The Ethics committee approved the study for a duration of 1-year. During this study period, 111 patients were screened and 53 patients were randomized from January 8, 2021 until January 26, 2022 (Fig. 1). Baseline characteristics and intraoperative data were well balanced between groups (Tables 1 and 2). Over the 2-hour study period, the percentage of study time with MAP in target was greater in the CLV group than in the control group. (Table 3, Fig. 2) Percentage time with MAP under 80 mmHg and MAP under 65 mmHg were both lower in the CLV group. There was no difference in the incidence of hypertension, total dose of norepinephrine, total volume of infused fluids, or postoperative LOS (Table 3). No failure of CLV controller was observed during the CLV cases.

4 Discussion

The CLV controller maintained MAP in target twice as often as manual control and reduced the incidence of MAP below 80 mmHg by 25% in our study population. These results are

consistent with previous perioperative reports [3-5]. Despite blood pressure management improvement, there was no difference in postoperative outcome. However, the study was not powered for this outcome and the study protocol duration was limited to the first two postoperative hours. One important limitation concerns the blood pressure target. A MAP target between 80 and 90 mmHg is quite high in comparison to clinical routine, which might have contributed to the lower in target time of the control group. ICU nurses may have been used to targeting lower values, and there may have been a learning curve during the study period. Another limitation is that a single investigator was in the patient's room during the entire study period. This was done for safety reasons and may limit the generalizability of our results. In patients admitted to the ICU after high-risk abdominal surgery, closed-loop control of norepinephrine infusion better maintained a MAP target of 80 to 90 mmHg and significantly decreased postoperative hypotensive when compared to manual norepinephrine titration. If further research will include patients during their entire perioperative care, it may be possible to determine if automated maintenance of tight MAP can improve patient outcome.

Acknowledgements

The authors would like to thank the nursing and medical staff of the Paul Brousse Liver and Biliary Center and the Kremlin-Bicêtre Hospital.

Data availability

By contacting corresponding author.

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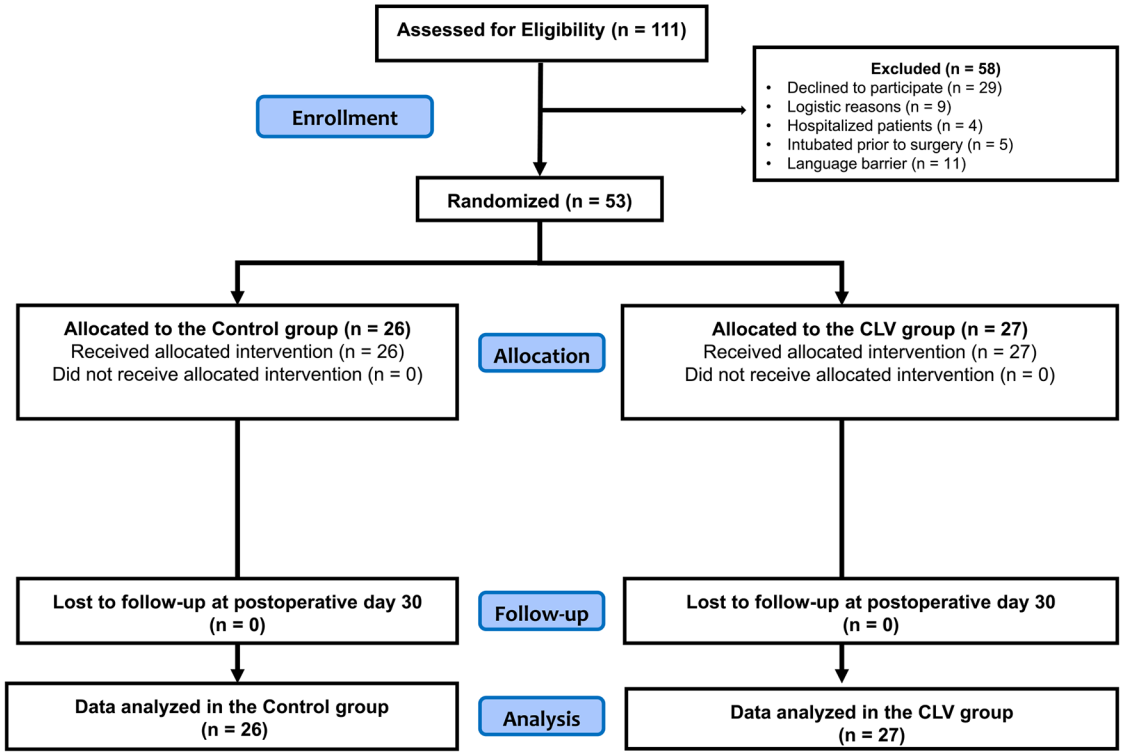

Fig. 1.
Patient inclusion flowchart

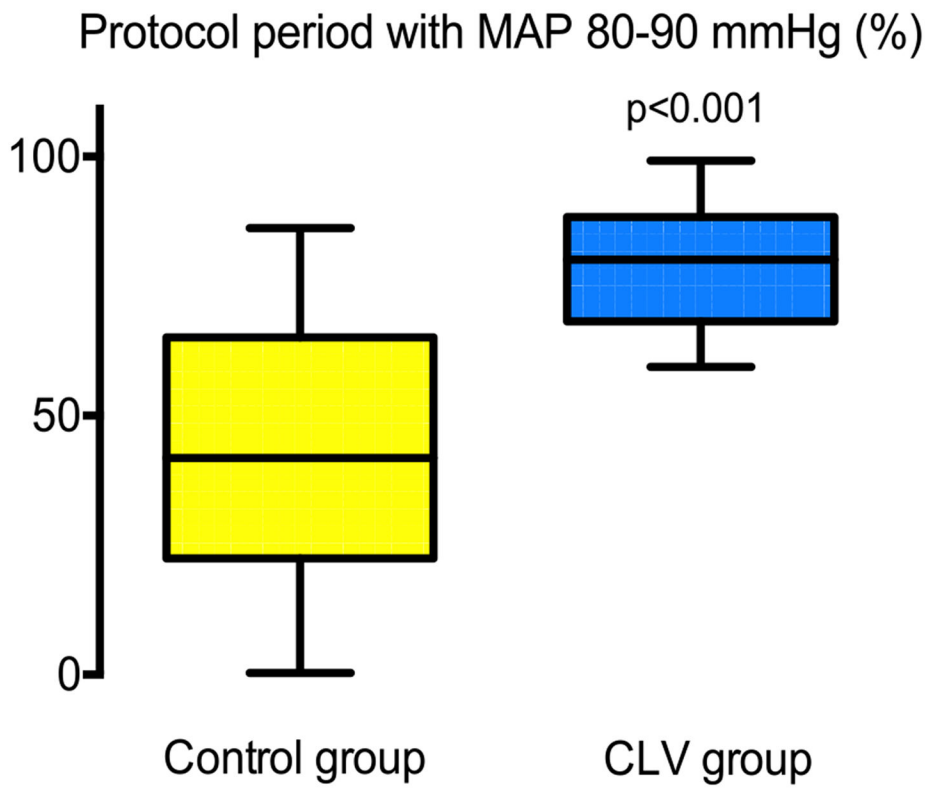

Fig. 2.
Percent time of Mean Arterial Pressure in target

Table 1

Baseline characteristics

Variables	Control group (N = 27)	CLV group (N = 26)
Age (year)	56 ± 19	58 ± 9
Male (%)	21 (78)	21 (81)
Body mass index (kg m^{-2})	24 [20–28]	28 [24–31]
ASA physical status III/IV	23 (85)/4 (15)	22 (85)/4 (15)
Preoperative hemoglobin (g dl^{-1})	10.9 ± 1.8	12.3 ± 12.5
Preoperative creatinine (μmol l^{-1})	77 [55–97]	83 [66–122]
Medications, n (%)		
Aspirin	4 (14)	2 (8)
β-blocker	9 (33)	13 (50)
Angiotensin-converting-enzyme inhibitor	3 (11)	2 (8)
Statin	1 (4)	3 (11)
Diuretic	9 (33)	7 (27)
Calcium blocker	4 (15)	6 (23)
Hypoglycemic agent and/or insulin I.V	6 (22)	6 (23)
Comorbidities, n (%)		
Ischemic heart disease	1 (4)	0 (0)
Arterial hypertension	12 (44)	15 (58)
Hyperlipidemia	0 (0)	3 (12)
Heart Failure	2 (7)	0 (0)
Atrial fibrillation	2 (7)	2 (8)
Stroke	1 (4)	0 (0)
Chronic renal insufficiency	3 (11)	5 (19)
Diabetes	10 (38)	9 (33)
Chronic obstructive pulmonary disease	14 (15)	1 (4)
Type of surgery, n (%)		
High-risk abdominal or urological surgery[a]	7 (26)	6 (24)
Liver transplantation	20 (74)	20 (76)

Data are listed as number and (%)”or mean ± standard deviation or median and [25th–75th] percentiles

J Clin Monit Comput. Author manuscript; available in PMC 2024 August 14.

ASA American Society of Anesthesiology physical status

[a]Include: major liver surgery, whipple surgery and total cystectomy

Table 2

Intraoperative data

Variables	Control group (N = 27)	CLV group (N = 26)	P value
Anaesthesia duration (min)	480 [438–540]	540 [448–633]	0.311
Surgery duration (min)	420 [360–480]	420 [360–531]	0.612
Total crystalloid (ml)	4000 [2250–5000]	4500 [3500–5500]	0.192
Albumin (ml)	1000 [1000–2000]	1750 [1125–2375]	0.220
Packed red blood cell (ml)[a]	750 [500–1000]	1000 [875–1625]	0.133
Fresh frozen plasma (ml)[a]	1000 [750–1500]	875 [688–1125]	0.398
Total IN (ml)	6000 [4500–8000]	6250 [5000–8125]	0.398
Estimated blood loss (ml)	1500 [600–1900]	1225 [800–2825]	0.631
Urine output (ml)	710 [450–1180]	905 [360–1105]	0.606
Total OUT (ml)	2135 [1240–3000]	2290 [1815–4278]	0.388
Total dose of norepinephrine (mg)	2.9 [2.0–5.1]	3.3 [2.8–3.9]	0.124
Lactate post-induction (mmol/l)	1.2 [0.8–1.6]	1.2 [0.9–1.8]	0.413
Lactate end of surgery (mmol/l)	2.7 [2.1–4.1]	3.4 [2.2–4.7]	0.255
Lactate ICU arrival (mmol/l)	2.0 [1.3–3.8]	2.1 [1.5–3.7]	0.742
Lactate 2 h post ICU arrival (mmol/l)	1.8 [1.2–2.9]	2.2 [1.1–3.2]	0.539

Data are expressed as number and (%), mean ± standard deviation or median and [25th–75th] percentiles

[a]For patients who were transfused

J Clin Monit Comput. Author manuscript; available in PMC 2024 August 14.

Table 3

Outcome data

Variables	Control group (N = 27)	CLV group (N = 26)	P value
Primary outcome			
Percentage of study period with a MAP between 80 and 90 (%)	41.8 [22.4–65.1]	80.2 [68.2–88.3]	< **0.001**
Secondary outcomes			
Percentage of protocol period with MAP > 90 mmHg (%)	13.8 [1.7–31.8]	16.4 [8.0–30.5]	0.715
Percentage of protocol period with a MAP < 80 mmHg (%)	26.4 [15.9–75.3]	1.1 [0.0–4.9]	< **0.001**
Percentage of protocol period with a MAP < 65 mmHg (%)	0 [0–4]	0 [0–0]	**0.017**
Total dose of norepinephrine during the study period (mg)	1.2 [1.1–1.4]	1.1 [1.1–1.2]	0.090
Total I.V fluid received during the study period (ml)	1250 [1000–1500]	1250 [1100–1500]	0.873
Exploratory outcomes			
Stroke volume index during the study period (ml. m^{-2})	48 ± 10	47 ± 11	0.833
Cardiac index during the study period (l. min^{-1} m^{-2})	3.7 ± 1.2	3.3 ± 0.8	0.163
Stroke volume variation during the study period (%)	8 [6–13]	7 [5–8]	0.943
Mean arterial pressure during the study period (mmHg)	84 [78–86]	88 [86–89]	**0.003**
Patients with any major complications	12 (44)	13 (50)	0.164
Patients with any minor complications	14 (52)	17 (65)	0.406
Length of stay in the intensive care unit (hours)	86 [44–117]	68 [38–121]	0.522
Length of stay in the hospital (days)	19 [15–29]	16 [12–21]	0.135

Data are expressed as number and (%), mean ± standard deviation or median and [25th–75th] percentiles

Statistically significant *P* values are indicated in bold