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Control of mean arterial pressure using a closed-loop system for norepinephrine infusion in severe brain injury patients: the COMAT randomized controlled trial

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Abstract

Brain injury patients require precise blood pressure (BP) management to maintain cerebral perfusion pressure (CPP) and avoid intracranial hypertension. Nurses have many tasks and norepinephrine titration has been shown to be suboptimal. This can lead to limited BP control in patients that are in critical need of cerebral perfusion optimization. We have designed a closed-loop vasopressor (CLV) system capable of maintaining mean arterial pressure (MAP) in a narrow range and we aimed to assess its performance when treating severe brain injury patients. Within the first 48 h of intensive care unit (ICU) admission, 18 patients with a severe brain injury underwent either CLV or manual norepinephrine titration. In both groups, the objective was

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Declarations

Conflict of interests Maxime Cannesson, Alexandre Joosten, and Joseph Rinehart are consultants for Edwards Lifesciences, Irvine, CA, USA. Maxime Cannesson, Joseph Rinehart and Alexandre Joosten have ownership interest in Perceptive medical which has developed the studied closed-loop vasopressor system. The other authors declare that they have no conflicts of interest concerning this article. Edwards and Perceptive Medical provided no direct or indirect funding in support of the current work.

to maintain MAP in target (within ± 5 mmHg of a predefined target MAP) to achieve optimal CPP. Fluid administration was standardized in the two groups. The primary objective was the percentage of time patients were in target. Secondary outcomes included time spent over and under target. Over the four-hour study period, the mean percentage of time with MAP in target was greater in the CLV group than in the control group (95.8 ± 2.2% vs. 42.5 ± 27.0%, $p < 0.001$). Severe undershooting, defined as MAP < 10 mmHg of target value was lower in the CLV group (0.2 ± 0.3% vs. 7.4 ± 14.2%, $p < 0.001$) as was severe overshooting defined as MAP > 10 mmHg of target (0.0 ± 0.0% vs. 22.0 ± 29.0%, $p < 0.001$). The CLV system can maintain MAP in target better than nurses caring for severe brain injury patients.

Keywords

Arterial pressure; Hemodynamics; Automation; Perfusion pressure; Neurocritical care

1 Introduction

Brain injury patients require optimal mean arterial pressure (MAP) targeting and stability to ensure adequate cerebral perfusion pressure (CPP) in the immediate post-injury period. This task frequently requires a vasopressor infusion that is hand titrated by intensive care unit (ICU) nurses. While optimal MAP values remain uncertain, studies have highlighted the difficulty of maintaining MAP targets within desired ranges, with both over- and under- treatment increasing the risk of complications [1]. On the one hand, several observational studies have found strong associations between hypotension and adverse events in ICU patients [2–5]. One the other hand, unnecessary vasopressor infusion can increase intracranial pressure (ICP), leading to cerebral ischemia or intracranial hemorrhage that compromise CPP. Thus, tight and accurate vasopressor titration is crucial in severe brain injury patients.

Current practice in brain injury patients is to set a target for MAP to achieve satisfactory CPP and instruct nurses to titrate the minimum infusion rate required to maintain that target. However, this approach is sub-optimal for several reasons: (1) the infusion is titrated at unpredictable and potentially infrequent intervals depending on a variety of nurse, workflow, and patient factors; (2) there may be significant lag time between changes in MAP and infusion rate; (3) additional work is created for the nursing team for a non-cognitive task. The end result is that patients may spend > 50% of treatment time outside of predefined MAP target ranges [6].

We have developed a closed-loop vasopressor (CLV) controller system that automatically adjusts norepinephrine infusion to correct hypotension [7–9]. We have recently shown that this system is vastly superior to manual titration of norepinephrine in prospective randomized controlled trials of high-risk patients during the perioperative period [10–12]. However, no study has to date evaluated neurocritically ill patients.

We thus conducted this single-center, two-arm, parallel-group, randomized controlled trial of severe brain injury patients to determine if the use of a norepinephrine CLV system would

result in more time spent with a MAP “in target” (MAP ± 5 mmHg of the predefined target MAP) compared to standard norepinephrine titration.

2 Methods

This study was approved on March 26, 2019 by the Comité de Protection des Personnes Sud Mediterrannée III (reference 2019.02.04 bis_19.01.03.70606) and registered with ClinicalTrials.gov (NCT03991052 on June 19, 2019) before the beginning of the study. The study was conducted in the Surgical ICU of Bicêtre Hospital from December 4, 2019 to January 27, 2023. Written informed consent was obtained from each patient’s family and from the patient if he/she recovered. Importantly, we had the authorization to include patients in our study under an “emergency condition” and then ask the family to keep or not the data retrospectively (if not possible to reach the patient’s family before inclusion). We recruited severe brain injury patients (Glasgow score < 9 at ICU admission), intubated, ventilated, sedated, requiring norepinephrine infusion and equipped with an ICP monitoring during the first 48 h of ICU admission except those with a bilateral mydriasis at the initiation of critical care (in the ambulance and first hour of ICU arrival). Patients were randomized into the manual group, in which MAP was managed by handtitration of norepinephrine by ICU nurses or in the CLV group, where an automated closed-loop system titrated norepinephrine. The study protocol began any time within the first 48 h of patient admission and lasted 4 consecutive hours during which sedation (propofol or midazolam and sufentanil infusions) remained unchanged. No anticipated CT scan was scheduled during this study period. Fluid administration was standardized in both groups and consisted of a baseline infusion of saline solution (84 ml. hour^{-1}) and fluid challenges of 250 ml of the same solution to optimize stroke volume index (SVI) using a real time clinical decision support system (Assisted Fluid Management) displayed on an advanced hemodynamic monitoring device (EV-1000 clinical platform, Edwards Lifesciences, Irvine, USA). The AFM system continuously determines when the patient may benefit from a fluid challenge, recommends fluid administration, and then analyzes the effects of the fluid challenge on SVI. [10, 13, 14]. In all patients, norepinephrine infusion was administered using an electric syringe pump in order to maintain MAP in “target” (within 5 mmHg of the prescribed range by the intensivist) while in the CLV group, the system automatically adjusted the norepinephrine infusion rate to maintain the MAP within the same range. Target MAP could of course vary during the study period (based on the observed ICP) and therefore, clinicians could change MAP target at any time during this period. Clinicians could also override the CLV system if MAP management was considered suboptimal. Importantly, the CLV system is designed to prevent errors in monitoring from affecting the dosing output of the system. Input is filtered for non-physiologic values, and if a value is out of range for more than a few seconds (i.e. an arterial line flush) the system will stop titrating and hold the dose constant until reliable monitoring resumes. Dampening is similarly detected through the pulse-pressure to mean pressure ratio, which holds relatively constant in subjects over time even as blood pressure changes.

Hemodynamic variables (MAP, heart rate, SVI, cardiac index, CPP and ICP) were recorded every 20 s by the EV1000 monitor or the patient’s monitor and subsequently averaged.

The primary objective was the percentage of the study period during which patients were in “target” (MAP ± 5 mmHg of the prescribed MAP). Secondary outcomes included the percentage of time patients were hypotensive (defined by a MAP of 5 mmHg or more below the chosen target), hypertensive (defined as a MAP > 5 mmHg or more above the chosen target). Importantly, MAP outside of target zone was predefined as “mild” if MAP was above or under 5 mmHg of the desired MAP target. Time above or under 10 mmHg of the target value was referred to as “severe”. Mean CPP, ICP, SVI, and cardiac index over the study period were also reported as well as the percentage of study period with an ICP > 20 mmHg and a CPP < 60 mmHg. Lastly, amounts of fluid and norepinephrine received during the study period were also recorded.

Variables are presented as either mean ± standard deviation or median with 25–75th percentiles or as a count with relevant percentage values. Group comparisons are made with Student t-test or Mann–Whitney U test when appropriate.

Our database from Bicetre Hospital indicated that brain injury patients spent 52 ± 17% of the time with a MAP within ± 5 mmHg of a MAP target. We therefore estimate that to have a power of 90% to demonstrate by non-parametric Mann–Whitney test a 50% improvement in the CLV group on the primary endpoint, it will only be necessary to include 10 patients per group. As we expected many drop outs and wanted a larger sample for robustness, we decided to randomize 48 patients in total (Figs. 1 and 2).

3 Results

Between March 26, 2019 and January 27, 2023, 23 patients were randomized (13 in the control group and 10 in the CLV group). After randomization, four patients’ families in the CLV group and one in the control group refused the use of the patient’s data. As a result, data of 6 CLV patients were compared with 12 control patients. The study was stopped prior to obtaining the sample size goal (N = 48) due to extreme recruitment difficulties posed by the beginning of the COVID period (Fig. 1). Baseline characteristics were similar between groups (Table 1).

The mean MAP pressure over the study period was 88 ± 8 mmHg in the CLV group versus 89 ± 11 mmHg in the manual group. Initial target MAP was 87 ± 5 mmHg and 88 ± 5 mmHg in the CLV and control group respectively (p = 0.751).

Patients in the CLV group spent a significantly higher study period in “target” compared to the control group (95.8 ± 2.2% vs 42.5 ± 27.0%; p < 0.001). They also spent a significantly lower study period with 5 mmHg or more under “target” (or “mild hypotension”) and 5 mmHg or more above target (or “mild hypertension”) when compared to the control group. Moreover, patients in the CLV group spent a significantly lower management time with 10 mmHg or more below target (or “severe” hypotension) and above target (or “severe” hypertension) when compared to the control group (Table 2, Fig. 2). Violin plots of each individual patient are presented in the Supplemental Figure.

4 Discussion

Consistent with our previous intraoperative and ICU studies, the CLV patients in this study spent more time in target and far less time in a hypotensive or iatrogenic hypertensive state. The CLV system made thousands of norepinephrine rate adjustments compared to four in median in the control group. As reported by three recent meta-analysis on the topic, a closed-loop system better maintains a variable in a narrow and desired range with less under- and over-shooting. [15–17] To date, two randomized controlled trials have studied this CLV system during perioperative care independently of any other intervention. [11, 12] In our present study, the CLV aimed to maintain MAP at an individualized level that the neuro-intensivist set to maintain ideal perfusion pressure and cerebral blood flow. Each patient thus had his or her own target. In the two previous studies, the target was the same for all patients: to avoid hypotension (defined as MAP below 65 mmHg). Although this difference in target does make comparisons between these studies a little more subtle, they all parallel one another by demonstrating that the CLV maintains MAP much more often in target than manual titration. The present study is of course neither designed nor powered to assess the impact of our CLV on patient outcome. Our aim was simply to confirm that the CLV titrates norepinephrine better than nurses in neurocritically ill patients. Although the study had to be prematurely stopped because of recruitment issues, it was still able to reach the statistical strength needed to find a significant difference between groups. In conclusion, our CLV system maintains MAP in target with automated adjustments of norepinephrine infusion better than ICU nurses caring for severe brain injury patients. By maintaining its target, it reduces mild and severe hypotension as well as hypertension. As hypotension increases the risk of cerebral ischemia and hypertension increases intracranial pressure, there is a solid physiological argument to further study this tool with randomized controlled trials evaluating outcome in patients suffering from severe brain injury. Closed-loop vasopressor infusions have been shown to be effective in managing blood pressure in a variety of settings, but to date there has been limited data in the ICU setting. Automated titration of vasoactive medications may be a promising tool for the future of critical care [18–20].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The datasets analyzed in this study are available from the corresponding author upon request.

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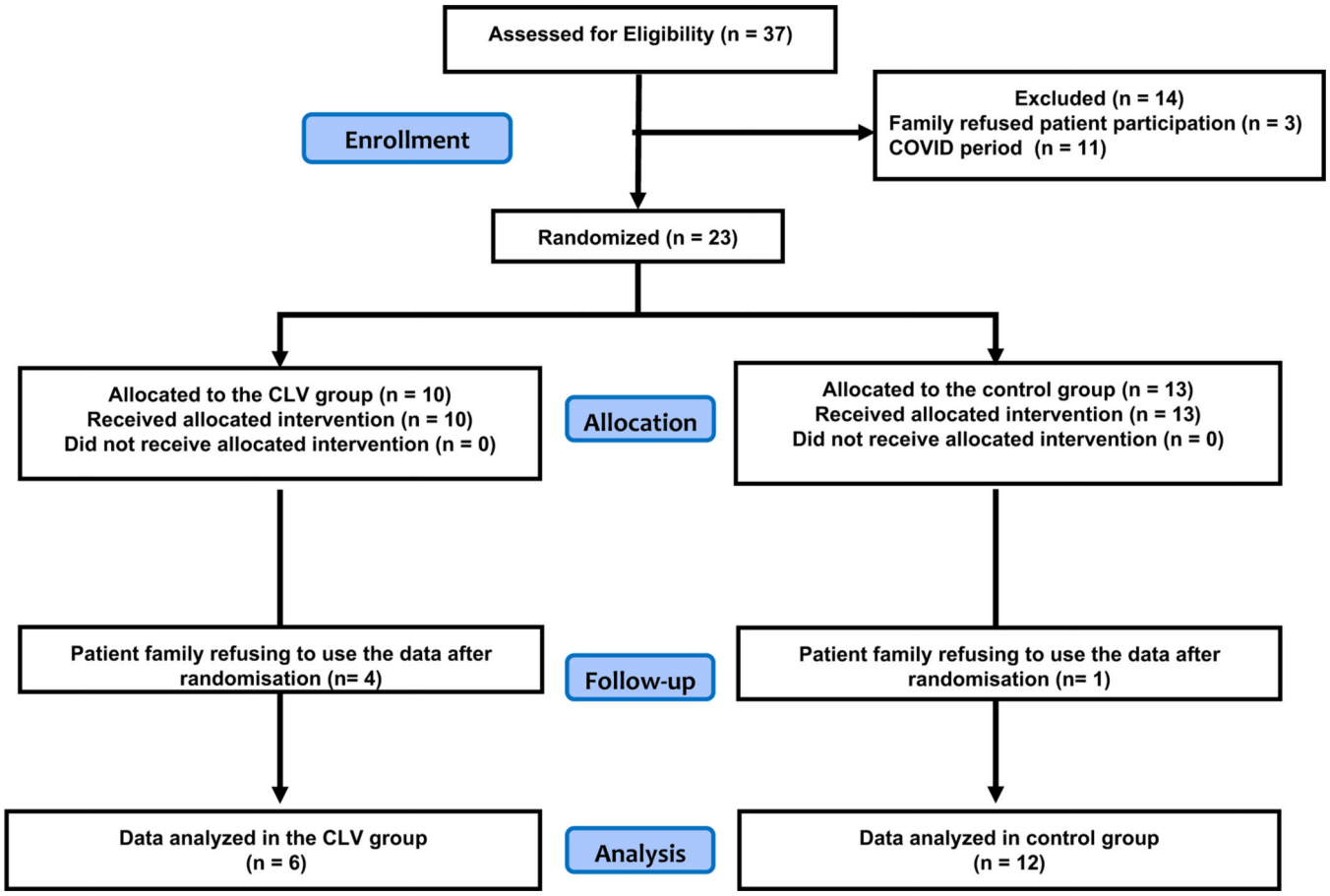

Fig. 1.
Flow chart

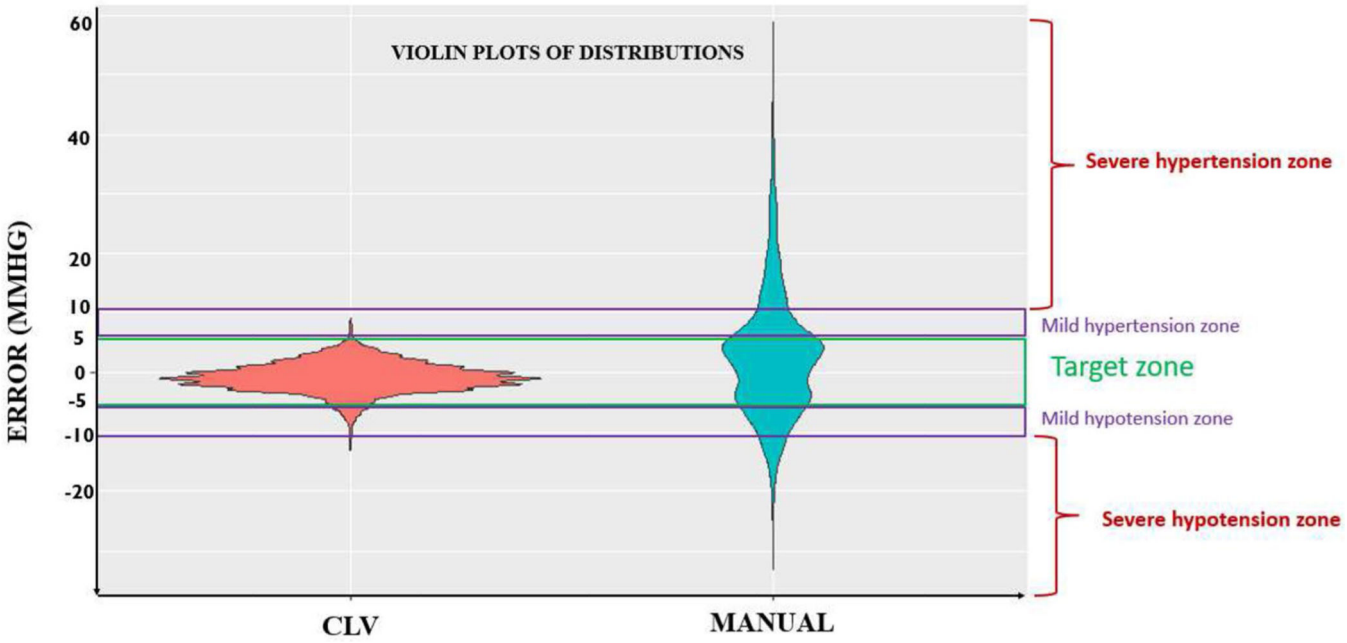

Fig. 2.

Violin plots of distribution of mean arterial pressure error in both groups. Target zone was defined as the time spent with a MAP within ± 5 mmHg of the desired MAP

Table 1

Baseline characteristics

Variables	CLV Group (N = 6)	Control group (N = 12)
Age (year)	55 [36–71]	41 [25–52]
Sex, Male (%)	5 (83)	8 (67)
Weight (kg)	78 [68–84]	75 [70–80]
Height (cm)	173 [170–179]	175 [173–180]
Cause of ICU admission Head trauma, N (%)	4 (67)	8 (67)
Subarachnoid hemorrhage, N (%)	2 (33)	4 (33)
Pulsatility index middle cerebral artery (right side) $	1.4 [1.3–1.7]	1.5 [1.2–2.2]
Pulsatility index middle cerebral artery (left side) $	1.7 [1.4–1.9]	1.7 [1.2–2.4]

$ before the beginning of the study protocol

Table 2

Outcome data

Variables	CLV group (N = 6)	Control group (N = 12)	P value
Primary outcome Percentage of study period "in target" (MAP ± 5 mmHg of the target)	95.8 ± 2.2	42.5 ± 27.0	< **0.001**
Secondary outcomes Percentage of study period with MAP < 5 mmHg of the target	3.7 ± 2.3	22.0 ± 25.0	< **0.001**
Percentage of study period with MAP > 5 mmHg of the target	0.5 ± 0.7	36.0 ± 30.3	< **0.001**
Percentage of study period with a MAP < 10 mmHg of the target	0.2 ± 0.3	7.4 ± 14.2	< **0.001**
Percentage of study period with a MAP > 10 mmHg of the target	0.0 ± 0.0	22.0 ± 29.0	< **0.001**
Total dose of norepinephrine during the study period (mg)	2.0 [1.8–2.0]	2.8 [2.2–3.1]	0.113
Number of norepinephrine infusion modification, N	1199 [1191–1204]	4 [3–7]	**0.002**
Total I.V fluid received during the study period (ml)	1083 ± 254	1104 ± 347	0.962
Baseline I.V fluid during the study period (ml)	336 ± 0	336 ± 0	> 0.999
Total fluid challenge during the study period (ml)	750 ± 185	833 ± 204	0.393
Stroke volume index during the study period (ml. m^{-2})	49 [45–63]	45 [42–50]	0.241
Cardiac index during the study period (l. min^{-1} m^{-2})	3.8 [3.5–4.2]	3.3 [2.9–3.7]	0.348
Intracranial pressure (ICP) during the study period mmHg)	15 [12–19]	14 [10–18]	0.743
Percentage of the study period with an ICP > 20 mmHg (%)	0.0 [0.0–5.6]	0.5 [0.0–4.4]	0.644
Cerebral perfusion pressure (CPP) during the study period (mmHg)	74 [70–76]	78 [73–84]	0.151
Percentage of study period with CPP < 60 mmHg	0.1 [0.0–0.4]	1.0 [0.0–7.0]	0.090

Data are presented as number and percentage, mean ± standard deviation or median and [25–75th] percentiles

Values in bold are statistically significant