Observational Study

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Clevidipine use after first-line treatment failure for perioperative hypertension in neurosurgical patients

A single-center experience

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Abstract

Perioperative hypertension is a common occurrence in the neurosurgical population, where 60% to 90% of the patients require treatment for blood pressure (BP) control. Nicardipine and clevidipine have been commonly used in neurocritical settings. This retrospective, observational study assessed the effectivity of the administration of clevidipine after nicardipine treatment failure in neurosurgical patients.

We retrospectively reviewed the medical charts of adult patients who were admitted to our neurosurgical department and received clevidipine after nicardipine treatment failure for the control of BP. The primary effectivity outcome was the comparison of the percentage of time spent at targeted SBP goals during nicardipine and clevidipine administration, respectively.

A total of 12 adult patients treated with clevidipine after nicardipine treatment failure and were included for data analysis. The median number of events that required dose-titration was 20.5 vs 17 during the administration of nicardipine and clevidipine, respectively ($P = .534$). The median percentage of time spent at targeted SBP goal was 76.2% during the administration of nicardipine and 93.4% during the administration of clevidipine ($P = .123$).

Our study suggests that clevidipine could be an alternative effective drug with an acceptable benefit/risk ratio in the neurosurgical population that fails to achieve BP control with nicardipine treatment.

Abbreviations: ASA = American Society of Anesthesiologist, BMI = body mass index, BP = blood pressure, CCB = Ca^{2+} channel blockers, FDA = Food and Drug Administration, IARS = International Anaesthesia Research Society, ICH = intracranial hemorrhage, ICP = intracranial pressure, IS = ischemic stroke, SAH = subarachnoid hemorrhage, SBP = systolic blood pressure.

Keywords: clevidipine, hypertension, neurosurgical, nicardipine, perioperative

1. Introduction

Perioperative hypertension is a common occurrence in the neurosurgical population, where 60% to 90% of the patients require treatment for blood pressure (BP) control.[1–3] Acute hypertension can affect the brain's capability to autoregulate blood flow and could lead to cerebral edema and increased intracranial pressure (ICP). Contrariwise, hypotension could extend ischemic damage in hypoperfused brain tissue, triggering cerebral vasodilatation and ICP plateau waves.[4] Therefore, precise, targeted BP management is essential and recommended in patients with acute neurological injuries in order to avoid severe adverse outcomes, such as hemorrhagic conversion, cerebral edema, hematoma extension, increased intracranial pressure, reperfusion injury, renal failure, encephalopathy, neurocognitive dysfunction, cerebral vasospasms, and/or cardiac complications.[1,2,5–9] Several authors suggest different systolic BP goals to treat patients undergoing acute neurological injuries and it varies according to the type of injury.[2,7] The recommended target systolic blood pressure (SBP) for intracranial hemorrhage (ICH) is <140 mm Hg, <160 mm Hg for subarachnoid hemorrhage (SAH) and <180 mm Hg for acute ischemic stroke (IS).[2,7] Clinical cerebral vasospasm is usually described in the setting of delayed brain ischemia or initial brain injury when the patient progresses to focal neurologic impairments secondary to poor blood flow in the area of the affected

Editor: Bernhard Schaller.

The abstract of this paper was presented at the 2019 International Anaesthesia Research Society (IARS) Annual Meeting and International Science Symposium in Montreal, Canada as a poster presentation with interim findings. The poster's abstract was published on 2019 IARS schedule website (http://iars.org/wp-content/uploads/IARS-2019-Annual-Meeting-Program.pdf).

This study was not financially supported. The authors declare no potential conflict of interest.

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How to cite this article: Borrell-Vega J, Uribe AA, Palettas M, Bergese SD. Clevidipine use after first-line treatment failure for perioperative hypertension in neurosurgical patients: A single-center experience. Medicine 2020;99:1(e18541).

Received: 2 August 2019 / Received in final form: 4 November 2019 / Accepted: 28 November 2019

http://dx.doi.org/10.1097/MD.0000000000018541

vessels.[9] Therefore, vascular smooth muscle cell dilators such as Ca^{2+} channel blockers (CCB) have been widely used for high BP management and cerebral vasospasm prophylaxis in neurosurgical settings.[9–11]

Nicardipine and clevidipine have been commonly used in neurocritical settings due to their outstanding pharmacodynamics, pharmacokinetic, safety, and efficacy profiles.[7,11] Clevidipine was approved in August 2008 by the US Food and Drug Administration (FDA) as an intravenous infusion, with an initial dose of 1 to 2 mg/hour. This dose can be initially doubled every 90 seconds until reaching targeted BP goals and thereafter should be titrated every 5 to 10 minutes.[12] The most common maintenance dose is 4 to 6 mg/hour.[12] The pharmacokinetic and pharmacodynamic profiles of clevidipine are characterized by their rapid-onset of action, linear dose-response, steady-state of arterial and venous levels and a peak pharmacodynamic BP response of 2 and 10 minutes after infusion initiation.[12,13]

Despite the use of nicardipine as first-line agent for perioperative hypertension management and the use of clevidipine after nicardipine treatment failure at our institution, the use of clevidipine in the neurocritical population has been shown to be safe and effective due to its rapid BP reduction effect and potential benefit of limiting hematoma expansion in patients with ICH.[1,2,5,14] This retrospective, observational study aims to assess the effectivity of the administration of clevidipine after nicardipine treatment failure in neurosurgical patients.

2. Methods

A single-center retrospective chart review was approved by the Institutional Review Board of The Ohio State University, Office of Responsible Research Practices. We retrospectively reviewed the medical charts of adult patients who were admitted to our neurosurgical department between October 1, 2015 and October 31, 2018 and received clevidipine after nicardipine treatment failure for the control of BP. Subjects aged <18 years old, non-neurosurgical patients, prisoners and pregnant were excluded from the study. As part of our institutional guidelines, nicardipine was administered as a first-line single agent for perioperative hypertension therapy with an individually targeted SBP goal of <140 mm Hg for ICH, <160 mm Hg for SAH and <180 mm Hg for IS. Clevidipine was used in patients that failed to achieve BP control with nicardipine therapy according to the corresponding critical care team criteria.

The main reason for switching from nicardipine to clevidipine was based on clinician's criteria and the need for further BP reduction treatment after refractory high BP values at maximal doses of nicardipine (15 mg/hour). The primary effectivity outcome was the comparison of the percentage of time spent at targeted SBP goals during nicardipine and clevidipine administration, respectively. As secondary outcomes, total time of infusion, number of required dose-titration and safety outcomes after the administration of both drugs were investigated. Other secondary safety outcomes involved the percentage of time spent at hypotension (demarcated as SBP < 90 mm Hg) and the occurrence of tachycardia (demarcated as heart rate > 100 beats per minute) during the administration of each drug. The documented demographic and clinical characteristics were age, sex, body mass index (BMI), American Society of Anesthesiologist (ASA) physical status, diagnosis at admission, baseline BP (systolic and diastolic), and length of hospital stay.

2.1. Statistical analysis

Demographic and clinical characteristics were summarized using descriptive statistics. Paired comparisons between clevidipine and nicardipine use included time at target SBP, time of drug infusion and number of events that required dose titration. Comparisons were analyzed using a Wilcoxon Signed Rank test. Statistical analysis was performed using SAS/STAT statistical software (version 9.4 of SAS for Windows, SAS Institute Inc., Cary, NC).

3. Results

Forty six adult patients who received clevidipine after nicardipine treatment failure at The Ohio State University Wexner Medical

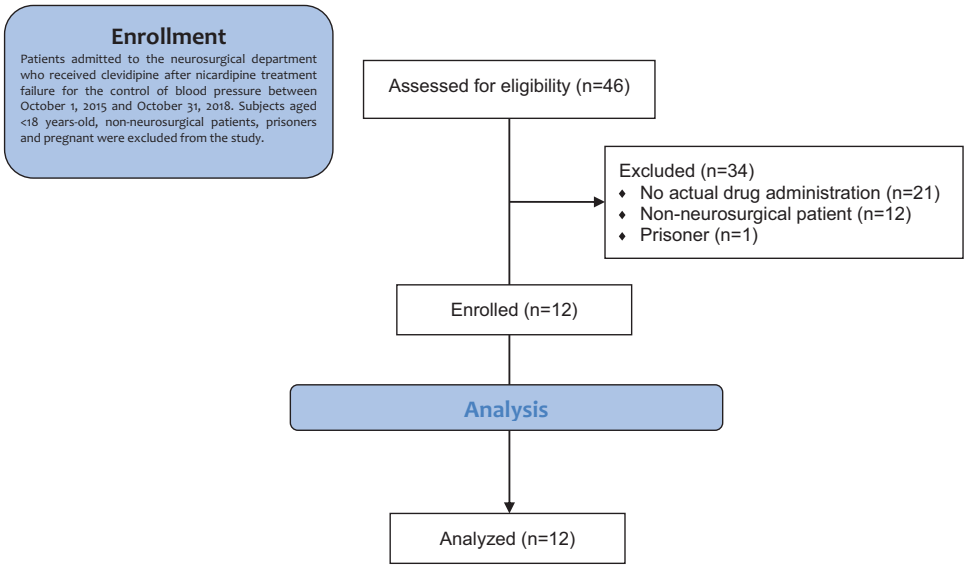

Figure 1. Trial profile according to CONSORT guidelines. Legend: n = number of subjects.

Table 1

Demographic and baseline characteristics.

Variables	Study group (n = 12)
Age, years, median (IQR)	52.5 (48.0, 57.5)
Sex, n (%)	
Male	4 (33%)
Female	8 (67%)
BMI, kg/m^2, median (IQR)	33.4 (25.0, 39.2)
ASA, n (%)	
I	0 (0%)
II	0 (0%)
III	4 (33%)
IV	8 (67%)
Race, n (%)	
Asian	1 (8%)
Black	2 (17%)
White	9 (75%)
Diagnosis at admission, n (%)	
Intracranial Abscess	1 (8%)
Intracranial Hemorrhage	7 (58%)
Ischemic Stroke	1 (8%)
Subarachnoid hemorrhage	3 (25%)
Baseline BP	
SBP, mmHg, median (IQR)	173.5 (159.0, 202.5)
DBP, mmHg, median (IQR)	98.5 (85.0, 112.0)
Length of stay, days, median (IQR)	25.9 (25.9, 34.1)

% = percentage, BP = blood pressure, DBP = diastolic blood pressure, IQR = interquartile range, mmHg = millimeter of mercury, SBP = systolic blood pressure.

Center from October 1, 2015 to October 31, 2018 were identified. Of these patients, 34 were excluded for not meeting eligibility criteria. The most common reasons for exclusion were as follows: drug ordered but not administered (n = 21), non-neurosurgical patients (n = 2) and prisoner (n = 1) (Fig. 1). A total of twelve adult patients treated with clevidipine after nicardipine treatment failure in the neurosurgical setting were included for data analysis.

The median age was 53 years-old (48.0–57.5). Seven patients (58%) were admitted for IH, and the median baseline SBP that required initial BP-lowering treatment was 173.5 mm Hg (IQR: 159.0–202.5). Additional demographic and baseline characteristics are summarized in Table 1.

During the study period (Table 2), the median infusion time of nicardipine was 52.9 hours and of 32.4 hours for clevidipine ($P = .007$). The median number of events that required dose-titration was 20.5 vs 17 during the administration of nicardipine and clevidipine, respectively ($P = .534$). The median percentage of time spent at targeted SBP goal was 76.2% (IQR: 51.0–93.3) during the administration of nicardipine and 93.4% (IQR: 73–100) during the administration of clevidipine ($P = .123$) (Fig. 2). Additionally, the median percentage of time spent with tachycardia (HR>100) was 13.1% during the administration of nicardipine and 2.2% during the administration of clevidipine ($P = .250$). Only 1 subject had events of hypotension (SBP < 90 mmHg) during the administration of both drugs.

Table 2

Effectivity and safety outcomes during BP-lowering treatment Effectivity and safety outcomes.

Variables	Nicardipine (n = 12)	Clevidipine (n = 12)	*P* value
Total time of Infusion, hours, median (IQR)	52.9 (22.0, 79.8)	32.4 (7, 43.3)	.007
Drug-titration events, n, median (IQR)	20.5 (12.0, 25.5)	17 (5, 29.5)	.534
Percentage time spent in targeted SBP,%, median (IQR)	76.2 (51.0, 93.3)	93.4 (73, 100)	.123
Percentage of time spent with tachycardia %, median (IQR)	13.1 (2.0, 35.7)	2.2 (0, 22.1)	.250

% = percentage, IQR = interquartile range, SBP = systolic blood pressure.

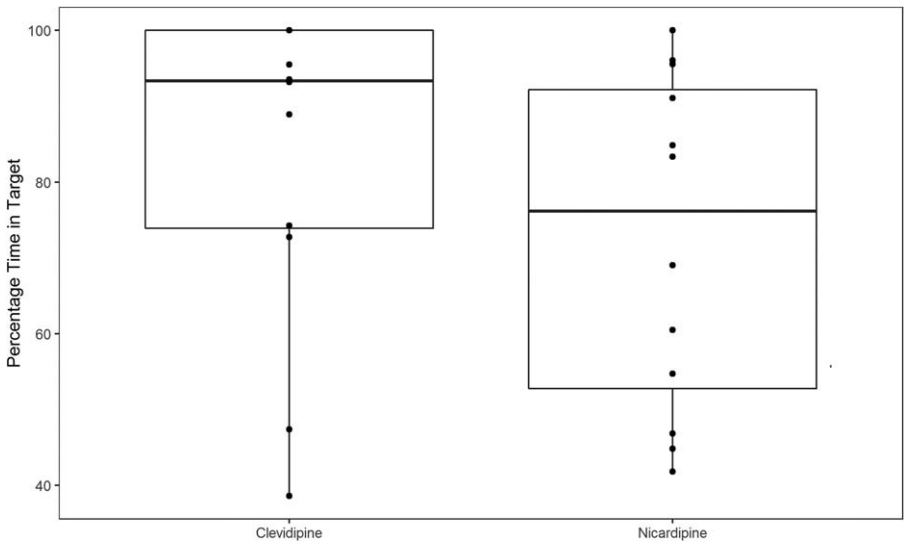

Figure 2. Percentage of time spent at targeted SBP goal.

4. Discussion

This retrospective observational study was conducted to assess the effectivity and safety of the use of clevidipine after nicardipine treatment failure in neurosurgical care patients requiring BP management. To date, this is the first study that evaluated the perioperative use of clevidipine after the failure of another intravenous BP-lowering treatment in this specific neurosurgical population. Our results suggested that clevidipine could be an effective alternative with a tolerable benefit/risk ratio in neurosurgical patients requiring acute control of BP management. Our data did not show a statistical difference of the primary outcome (percentage time spent in targeted SBP), but there was a significantly shorter length of the administration time required to achieve BP control with clevidipine, after nicardipine treatment failure and the percentage of time spent in the targeted SBP was slightly higher during clevidipine administration. It should be emphasized that this benefit has substantial clinical significance for this critical care population where patient deterioration could quickly progress to fatal outcomes. The safety analysis showed a similar incidence of adverse events for both drugs and a lower percentage of time spent in tachycardia during clevidipine administration. Therefore, the perioperative use of clevidipine as a second-line agent after the failure of nicardipine therapy should be considered as an effective and safe regimen for the management of acute hypertension in the perioperative setting of neurocritical patients.

Previous studies demonstrated the efficacy of clevidipine use in the neurosurgical population. A prospective single-arm study in neurosurgical patients with acute hypertension (The ACCELERATE trial) was carried out in patients with ICH (surgical and non-surgical patients). Clevidipine was administered within 6 to 12 hours after the onset of symptoms with an initial SBP target goal of $\leq$160 mm Hg and thereafter titrated to achieve a SBP target of 140 to 160 mm Hg.[14] The infusion of Clevidipine rapidly and safely reduced BP to the target SBP goal of 140 to 160 mm Hg within the first 30 minutes after the start of the infusion and potentially prevented further hematoma expansion.[14] The mean decrease in SBP was 10.8 mm Hg and 38.8 mm Hg at 3 minutes and 30 minutes of infusion, respectively, when compared to baseline values.[14,15] The results of our study showed a similar trend in a cohort treated with clevidipine which achieved an effective BP control with only a few episodes of tachycardia.

The efficacy and safety profile of clevidipine has been investigated in different clinical trials that included patients requiring acute hypertension management in the perioperative setting (ESCAPE 1, ESCAPE 2, and ECLIPSE).[16–18] The data from ESCAPE 1 and ESCAPE 2 trials revealed that the BP target goal was achieved at a median time of 6 and 5.3 minutes, respectively.[12,13] On the other hand, the ECLIPSE trial compared the data from three clinical trials that assessed the perioperative administration of clevidipine, nicardipine, sodium nitroprusside or nitroglycerin in patients undergoing cardiac surgery who required acute treatment of hypertension.[18] The results showed that clevidipine was more effective in controlling BP within a targeted range and had less BP excursions when compared with the other drugs.[18]

Finger et al conducted a retrospective analysis of 57 patients admitted to the neuroscience intensive care unit and compared the variance in time to achieve a target SBP goal between clevidipine and nicardipine administrations. Target SBPs varied between patients due to the varying etiology of intensive care admissions and were matched between the two groups. The authors concluded there was no statistically significant difference in BP management between the two agents (in terms of time for achieving a target SBP and percentage of time between certain BP ranges), although a trend towards shorter time to achieve the target existed within the clevidipine group (1 hour vs 2 hour). Significantly less volume administration was reported in the clevidipine group and the same incidence of hypotension and bradycardia events were reported in both groups.[5] Likewise our cohort shows similar results in addition to reduced time to control BP values.

Bekker et al. performed a prospective, single-arm trial evaluating the efficacy and safety of clevidipine in patients that underwent intracranial surgery. The efficacy was assessed by the proportion of patients not requiring rescue use of antihypertensive drugs to maintain a target SBP level of <130 mm Hg.[1] Safety was assessed by analyzing the frequency of the following drug-related adverse events: hypotension, bradycardia, tachycardia, and hypertension.[1] BP was well controlled with the monotherapy of clevidipine in 81% of the patients. Additional doses of labetalol ensured a complete response of BP-lowering effect in all patients.[1] In contrast, the patients in our study did not require additional antihypertensive drugs for BP management after the administration of clevidipine in monotherapy.

In another open-label prospective study conducted by Varelas et al., the efficacy and safety profile of clevidipine in the reduction of SBP before or after aneurysm clipping or coiling in patients with aneurysmal SAH were assessed.[19] The study showed a targeted SBP reduction goal (122–154 mm Hg) in all patients, which was achieved at 14.2 ± 2.55 minutes with an infusion rate of 10.8 ± 9.1 mg/hour[19] and an incidence of 17.5% and 11.8% of patients that exhibited SBP values below and above the targeted goal, respectively.[19] This study presented an interesting approach of the use of clevidipine and its efficacy/safety profile during a neurosurgical procedure.

Rosenfeldt et al conducted a retrospective chart review that compared patients with acute stroke (defined as IH, AIS or SAH) who were managed with nicardipine or clevidipine for acute hypertension.[7] The study showed no differences in any of the efficacy outcomes; 73.3% and 66.1% ($P=.39$) reached SBP goal within 1 hour, then 95% and 98.3% reached SBP goal within 6 hours in the nicardipine and clevidipine groups, respectively.[7] Additionally, there were no differences in the safety outcomes between both groups.[7] Hypotension events (SBP <120 mm Hg) occurred in 73% of patients who received nicardipine and 81% in those treated with clevidipine ($P=.29$), whereas 3.3% and 10.1% experienced severe hypotension (SBP <90 mm Hg) in the nicardipine and clevidipine groups ($P=.14$), respectively.[7]

Allison et al conducted a retrospective observational cohort study comparing the use of clevidipine and nicardipine in patients with AIS and ICH, and reported no differences in time from initiation of clevidipine or nicardipine to reach a targeted SBP goal (83 vs 103 minutes, respectively, $P=.101$).[2] Hypotension was exhibited in 7.1% and 10% ($P=.003$) of clevidipine and nicardipine patients, respectively.[2]

Another retrospective observational study conducted by Finger et al compared the difference in time to achieve targeted SBP after the administration of clevidipine vs nicardipine in patients admitted to neurological intensive care unit.[5] The study showed a median time to target SBP of 30 minutes and 36 minutes for the clevidipine and nicardipine groups, respectively, ($P=.13$) and the percentage of time spent in targeted SBP was 79 vs 78% ($P=.64$) in the clevidipine and nicardipine groups, respectively.[5] Our study showed a non-significant higher percentage of time spent in

targeted SBP in the patients treated with clevidipine compared to those who received nicardipine (93% vs 76% (P=.123).

We recognize a few limitations to be considered in our study. First, the study was not able to detect reliable statistical significance in the primary and most of secondary endpoints due to the retrospective design and the small sample size of the study. Second, the interval of time between vital signs assessments was highly variable and inconsistent in the investigated cohort, taking into account that the data relied on the nursing records. Therefore, the percentage of time spent in target SBP goals and in tachycardia was not precise, especially in patients that were not monitored with arterial line during the administration of both drugs. Third, another limitation from the retrospective nature of the study is the potential risk for human error during data collection and low quality of accessible data charted in the medical records. Fourth, despite the fact that clinicians and nurses properly followed institutional protocols for nicardipine and clevidipine administration in this neurocritical population, the total doses used and titration regimens in all patients were not considered in the statistical analysis due to the variability of this data. Finally, there could be other factors that we were not able to easily identify and/or measure such as other concomitant comorbidities, clinical deterioration, and optimal titration of the administration of both drugs, and/or pharmacodynamic considerations of the immediate administration of clevidipine after nicardipine discontinuation, without leaving a wash-out period.

5. Conclusion

Our study suggests that clevidipine could be an alternative effective drug with an acceptable benefit/risk ratio in the neurosurgical population that fails to achieve BP control with nicardipine treatment. Further prospective randomized trials investigating both drugs should be performed to achieve a better understanding of how to best provide perioperative management for high BP in the neurosurgical population.

Acknowledgments

The authors gratefully acknowledge Garegin Soghomonyan, B.S. c; Andrew Costa, B.S.c; Luis Periel, B.S.c and Kenna Koehler, M. D.c for their writing and editing collaboration (all of them provided authorization to be named on this publication).

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