Title: A retrospective cohort study comparing clevidipine and nicardipine for the management of blood pressure in acute aortic dissection in the emergency department

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Abstract

Objective: Intravenous calcium channel blockers are commonly used in combination with other agents to rapidly reduce systolic blood pressure (SBP) in suspected aortic dissection. Use of clevidipine in comparison to nicardipine in the emergency department setting has not been fully described, and is better understood in the context of cardiothoracic surgery. This study's goal was to compare the time to SBP goal utilizing clevidipine vs nicardipine in patients with suspected acute aortic dissection.

Methods: A single-center, retrospective, observational cohort study was conducted on patients for which an "Aorta Alert" was called who received either clevidipine or nicardipine. The primary outcome was time to reach goal SBP in the emergency department setting. Patient demographics, clevidipine doses, nicardipine doses, systolic blood pressures, and systolic blood pressure goal values were collected using both clinical progress notes and EPIC medication order information.

Results: Seventeen patients were included in the final analysis. Of the seven patients in the nicardipine group, five received nicardipine prior to ED arrival compared to one in the clevidipine group (p=0.009). There was no statistically significant difference in the primary outcome of median time to reach goal SBP (23 min vs 9 min, p=0.109) or mortality during the encounter (10% vs 0%, p=0.388).

Conclusions: No difference in time to goal blood pressure between nicardipine and clevidipine was identified. However, the small sample size of this study may have limited its ability to detect a difference if one exists. Clinical differences between the products still warrant additional investigation.

1. Introduction

The 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults recommends rapid blood pressure reduction in all cases of suspected acute aortic dissection with beta blockade and vasodilators to a goal SBP of ≤120 mmHg within 20 minutes.[1] Rapid blood pressure reduction is indicated whenever aortic dissection is suspected regardless of type or location of the dissection, however it should not delay surgical intervention if indicated.[2]

Clevidipine is a relatively new intravenous (IV) calcium channel antagonist which received FDA approval August 1, 2008 for management of acute hypertension.[3] Inhibition of calcium ion influx through L-type calcium channels in arterial smooth muscle during depolarization leads to a decrease in mean arterial pressure (MAP) via reduction in arteriolar vascular resistance.[4] Clevidipine has been shown to have a rapid onset of action, with MAP reductions of 5.9% within 2 minutes in patients with postoperative hypertension (given at an initial infusion rate of 0.4 mcg/kg/min).[5] Rapid dose titration of clevidipine as quickly as every 90 seconds results in systolic blood pressure SBP reduction of ≥15% from baseline being achieved in a median of 6 minutes in cardiac surgery patients with preoperative hypertension.[6]

Nicardipine is a calcium channel antagonist which comes in IV form as well, and is a well-established choice as a vasodilator in suspected acute aortic dissection.[2] While nicardipine has similar blood pressure lowering effects and a similar mechanism of action to clevidipine, its onset of action (10-15 min) and frequency of dose titration (every 5-15 min) are longer.[7]

The pharmacokinetic profile of clevidipine gives it the potential to be clinically useful in many different situations requiring acute blood pressure lowering. The current literature has described blood pressure control using clevidipine in cardiac surgery, intracranial surgery, and acute neurological injury but there is a paucity of data surrounding clevidipine's use for management of acute aortic dissection in the emergency department. The major determinants of dissection extension and rupture include systemic blood pressure and for of left ventricular contraction (dP/dt).[8] Controlling these variables as quickly as possible is therefore the primary goal of medical management of aortic dissection.[8] The literature that does analyze clevidipine's use in acute aortic dissection

compared it to sodium nitroprusside.[9] That study did not see a statistically significant difference in time to reach goal systolic blood pressure between clevidipine and sodium nitroprusside and found clevidipine was associated with lower drug costs measured by average wholesale price of total mg/day.[9] Sodium nitroprusside is not always a practical agent to use in the emergency department due to the time required to compound and prepare the dose. Clevidipine is available in a premixed bag making it an attractive option for use in the emergency department setting.

The University of Virginia Health System Emergency Department currently utilizes an "Aorta Alert" notification to quickly identify and treat patients who show signs and symptoms of possible aortic dissection. When an Aorta Alert is called either during transport to the hospital or in the Emergency department cardiothoracic surgeons, the charge nurse, and the ED pharmacist are notified to facilitate rapid evaluation and blood pressure management. Current practice typically involves utilizing intravenous beta receptor antagonist (e.g. esmolol) plus an intravenous calcium channel antagonist (either nicardipine or clevidipine). There is currently limited literature to guide physicians and pharmacists in deciding the preferred calcium channel antagonist to use in this population.

2. Methods

A single-center, retrospective, observational cohort study was conducted on patients for which an "Aorta Alert" was called who received either clevidipine or nicardipine in the ED from 1/1/2019 to 9/30/2019. Patients were excluded if they receive both nicardipine and clevidipine at any time during the study period. Patients receiving other IV antihypertensive agents prior to the study period or during the study period were included and the name of the IV antihypertensive was noted. The list of patients was compiled using archived "Aorta Alert" pages and information from the electronic health record (Epic® May 2019 version). Patient demographics, clevidipine doses, nicardipine doses, systolic blood pressures, and systolic blood pressure goal values were collected using both clinical progress notes and EPIC medication order information. The primary outcome, difference in time to SBP goal, was determined by analyzing the difference in time between initiation of calcium channel antagonist in the emergency department and achievement of blood pressure goal. Secondary outcomes were determined using clinical progress notes and hospital medication pricing information.

3. Statistical analysis

Primary and secondary outcomes were evaluated using a Mann-Whitney *U* test. Differences in baseline characteristics between groups were evaluated using a Chi-Square test as well as descriptive statistics. The sample size goal was based on similar trial data and sample size was limited due to pager record availability. Statistical significance was defined as $p<0.05$. Data were evaluated using IBM SPSS® Statistics version 26.

4. Results

Of the 38 patients assessed who triggered an Aorta Alert, 17 were included in the final analysis. The most common reason for exclusion was not receiving either study medication in the ED due to hypotension on arrival (n=9). Both groups were majority male (80% vs 86% in the clevidipine group and the nicardipine group, respectively) and the majority had a documented history of hypertension (60% vs 57%). Of the seven patients in the nicardipine group, five received nicardipine prior to ED arrival compared to one in the clevidipine group (p=0.009). There was no statistically significant difference in the primary outcome of median time to reach goal SBP (23 min vs 9 min, p=0.109) or mortality during the encounter (10% vs 0%, p=0.388). There was a statistically significant difference in incidence of study-defined hypotension (0% vs 43%, p=0.023). Based on average wholesale price (AWP) at the time the study was conducted, utilizing a clevidipine 25mg/50mL vial instead of a nicardipine 40mg/200mL premixed bag results in a 64% savings in drug cost.

5. Discussion

To date there has been no direct comparison of clevidipine and nicardipine for acute blood pressure lowering for suspected aortic dissection in the ED setting. Limiting aortic dissection extent and probability of rupture (and therefore the associated negative sequelae) requires swift and tightly controlled SBP lowering. There was not a statistically significant difference in either the median time to reach goal SBP or the SBP upon drug initiation in the ED. However the difference in pre-hospital treatment is noteworthy. There appeared to be an interaction between

pre-hospital antihypertensive choice and choice of agent in the ED (1 patient in the clevidipine group vs 5 in the nicardipine group received nicardipine pre-hospital, p=0.009).

The significant difference in hypotension found between the two groups is also notable. A point to be mentioned while examining this result is the study's definition of hypotension, which was any instance of SBP <100 mmHg in the ED. This definition was based on the definition used in a comparable trial, but may not be a clinically significant definition. The incidence of SBP <90 mmHg would have resulted in a 1 vs 0 comparison and not have been statistically significant. Without a larger sample size, greater conclusions cannot be drawn based on this result alone.

Due to the nature of the ED environment and the relatively small amount of drug administered during the study period, a full cost analysis was not undertaken. However the AWP of each unit of use product at the time of the study was noted and there were meaningful differences. None of the patients included used more than 1 bag or vial of product in the ED encounter, and therefore the cost differences in this setting rely on the cost of the unit of use rather than the total amount administered. It is reasonable in this situation to take drug unit cost into consideration when clinical outcomes differences between the two treatments in this setting and in others appear similar.

This study had several limitations. At this time, documentation interoperability between the IV pump and the HER is not present and therefore must be recorded manually. Similarly, all blood pressures must be documented manually by staff. The accuracy of this manual documentation directly impacts the primary outcome and is subject to error, bias, and incompleteness. Variations in pre-hospital care also may have influenced our primary outcome, with different emergency medical services (EMS) utilizing different protocols with different SBP goals. These variations could have also contributed to selection bias, with 9 patients receiving neither clevidipine nor nicardipine upon arrival to the ED due to hypotension and therefore being excluded from the study. Finally this trial was limited due to the small sample size, which may have hidden any statistically significant difference in primary outcome due to a single outlier or incomplete documentation. A larger trial would be needed to confirm this result.

6. Conclusion

Based on the study results, no difference in time to goal blood pressure between nicardipine and clevidipine was identified. However, the small sample size of this study may have limited its ability to detect a difference if one exists. The statistically significant difference in hypotension between groups is notable, but was influenced by the study definition of hypotension being any incidence of SBP <100 mmHg and may lack clinical significance. Clevidipine was noted to have cost advantages in the ED setting as compared to nicardipine premixed bags. In this small study, clevidipine did not show a statistically significant difference in time to goal SBP, but may confer a cost-savings advantage in certain situations. Clinical differences between the products still warrant additional investigation.

Figure 1. Study Enrollment Flowchart

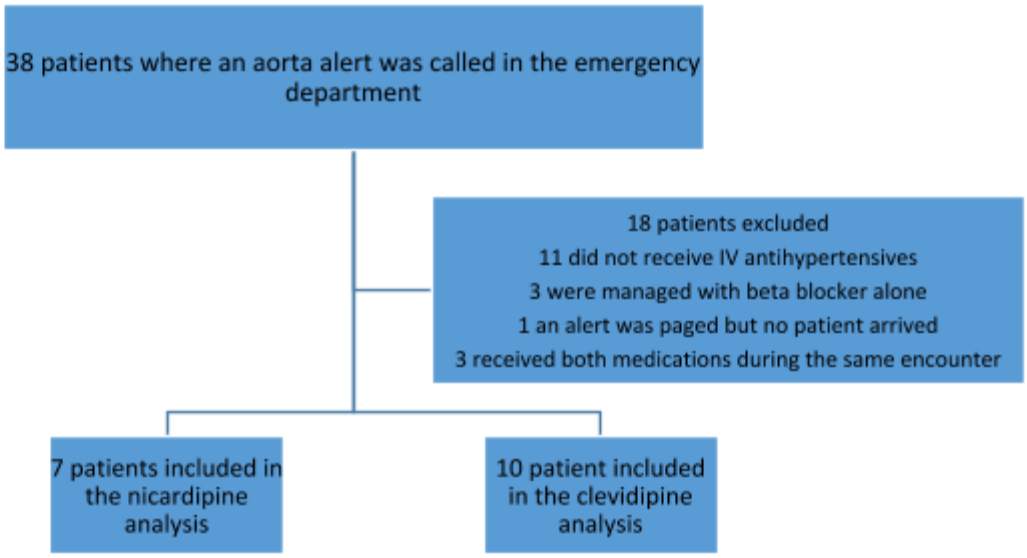
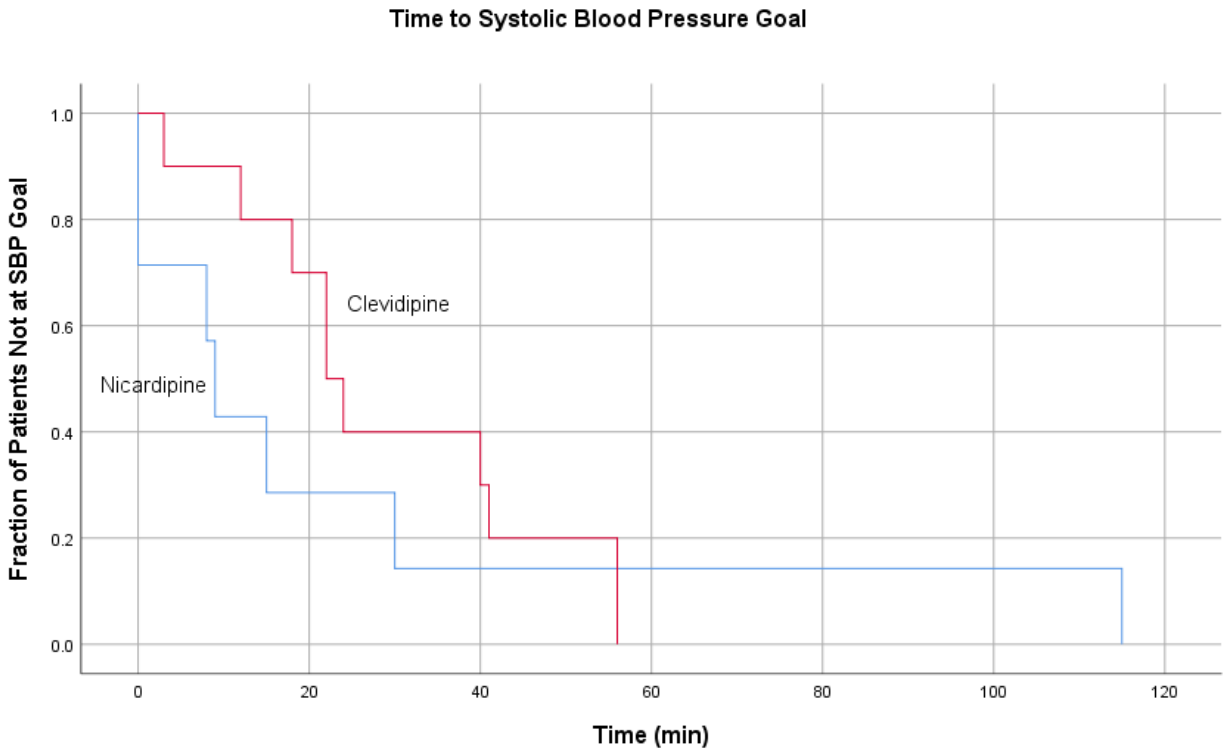


Table 1. Baseline characteristics, primary and secondary outcomes

	Clevidipine n=10	Nicardipine n=7	p-Value
Age (± SD)	73 ± 16	59 ± 13	0.319
Gender, male (%)	8 (80)	6 (86)	0.761
Aortic Dissection type A (%)	7 (70)	3 (42)	0.585
Documented history of hypertension (%)	6 (60)	4 (57)	0.906
Documented RPH response to bedside (%)	6 (60)	4 (57)	0.906
Median length of time spent in the Emergency Department, min	140	75	0.383
IV antihypertensive prior to arrival (%) Nicardipine Labetalol	3 (30) 1 (10) 2 (20)	5 (71) 5 (71) 0 (0)	0.092 0.009 0.208
SBP upon drug initiation in ED (± SD)	162 ± 38	141 ± 40	0.39
Lowest SBP in ED (± SD)	114 ± 6.5	104 ± 12	0.35
Hypotension	0 (0)	3 (43)	0.023
Median time to reach goal SBP, min	23	9	0.109
Mortality during encounter (%)	1 (10)	0 (0)	0.388
Median amount of drug administered during ED encounter, mg	4.5	7.4	*

Figure 2. Kaplan Meier time-to-event analysis



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