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Clevidipine versus sodium nitroprusside in acute aortic dissection: A retrospective chart review☆

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ABSTRACT

Aim: Intravenous vasodilators are often added to beta-blocking agents to reach blood pressure (BP) goals in aortic dissection. Control of BP using clevidipine has been described in hypertensive emergencies and cardiac surgery but not in aortic dissection. The aim of this study was to compare clevidipine versus sodium nitroprusside (SNP) as adjunct agents to esmolol for BP management in aortic dissection.
Methods: A single-center retrospective chart review evaluated patients diagnosed with aortic dissection. The primary outcome measure was time to reach patient specific systolic blood pressure (SBP_{PT}) goals after initiation of esmolol infusion. Efficacy of clevidipine and SNP was assessed using area under the curve analysis of positive and negative excursions outside of SBP_{PT} goals (AUC_{SBPe}). Cost data was calculated using average wholesale price in U.S. dollars.
Results: Fourteen patients were included in final analyses. Median systolic BP immediately prior to initiation of esmolol was 162 mm Hg vs 161 mm Hg for clevidipine and SNP groups, respectively ($p = 0.99$). Median time to reach SBP_{PT} goal was similar between clevidipine and SNP (1.68 versus 1.03 h [$p = 0.99$]). Median AUC_{SBPe} was similar for clevidipine and SNP (206.9 versus 538.9 mm Hg $*$ min $*$ hr^{-1} [$p = 0.11$]). Cost was significantly reduced using clevidipine versus SNP ($1223.28/day versus $7674.24/day [$p < 0.001$]).
Conclusions: Clevidipine administration during initial medical management of aortic dissection showed similar efficacy compared to SNP when used as adjunct therapy to esmolol. These data suggest clevidipine is a less costly, reasonable alternative to SNP in acute aortic dissection as adjunct therapy to esmolol. Further studies are needed to validate these results.

1. Introduction

Control of systolic blood pressure (SBP) and heart rate is paramount in the initial management of acute aortic dissection [1]. Patients benefit from intravenous (IV) beta-blockade to lower aortic wall stress by controlling velocity, rate of ventricular contraction and blood pressure (BP) [2]. Esmolol is an IV beta-blocker that may be titrated via continuous infusion, however; patients often require additional anti-hypertensive therapy to reach patient specific systolic blood pressure (SBP_{PT}) goals. Sodium nitroprusside (SNP) is an established vasodilator used for additional BP control in aortic dissection [3]. Acquisition costs for SNP have risen over 1900% since 2013 and have prompted institutions to re-evaluate its use compared to other IV anti-hypertensive infusions [4].

Clevidipine is an IV dihydropyridine calcium channel blocker; it is used to reduce BP when rapid titration is necessary [5]. Clevidipine selectively and potently vasodilates arterial circulation resulting in decreased systemic vascular resistance and mean arterial pressure (MAP). Clevidipine's onset of action is 2–4 min with a typical duration of effect of 5–15 min, giving it a similar pharmacologic profile to SNP [5,6].

Control of BP using clevidipine has been described in hypertensive emergencies and cardiac surgery [7-10]. The use of clevidipine to control BP in acute aortic dissection, however, has not been described. This study aims to evaluate and compare the use of clevidipine versus SNP as adjunct therapies to esmolol for BP control in acute aortic dissection, with time to SBP_{PT} as the primary outcome measure.

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2. Methods

This study was a single-center retrospective chart review conducted at an urban safety-net hospital with active interventional cardiology and cardiac surgery programs. This study was approved by the institutional review board at Hennepin County Medical Center. Patients were identified through a query of inpatient orders from September of 2010 to 2016 for either clevidipine or SNP with an accompanying new diagnosis of aortic dissection using International Classification of Diseases (ICD 9: 441xx; ICD 10: I71xx). Inclusion criteria included patients older than 18 years with newly diagnosed aortic dissection initiated on esmolol plus either clevidipine or SNP in the emergency department. Patients were excluded if esmolol, clevidipine, or SNP infusions was started at an outside hospital, if a continuous infusion of any anti-hypertensive therapy other than esmolol, clevidipine, or SNP was used, if SBP_{PT} was not reached prior to surgical management, if patients were pregnant or breastfeeding, or a final diagnosis of no aortic dissection was reached.

The primary outcome measure was time to reach SBP_{PT} goal after initiation of esmolol infusion based upon review of the electronic medication administration record (eMAR). Because BP goals are expected to differ among patients depending on concomitant disease states, SBP_{PT} was defined by the medical team caring for each patient and retrieved from electronic medical record (EMR). SBP_{PT} goal ranges in our institution vary between 10 and 20 mm Hg.

Additional data collected included basic demographics, vital signs, single bolus doses of anti-hypertensive drugs, area under the curve (AUC) analysis of both positive and negative excursions outside of SBP_{PT} goals (AUC_{SBPe}), infusion duration, and drug cost data. AUC_{SBPe} analysis was performed for 24 h after drug (clevidipine or SNP) initiation or until time of surgical management, whichever was less. Duration of infusion for secondary endpoint analysis for both AUC and cost was time from the start to the end of infusion or a maximum 24 h, whichever was less. AUC_{SBPe} was calculated for each patient, summated, normalized per hour and expressed as mm Hg $*$ min $*$ hr^{-1}; AUC calculations were performed using similar approaches to previously published literature [7]. Study drug costs in U.S. dollars were calculated using average wholesale price (AWP). For each patient, cumulative milligrams of study drug were calculated from the eMAR and normalized per 24 h. Costs were also evaluated using quantity of punctured clevidipine vials or SNP infusion bags taking into account stability for each preparation.

3. Statistical analysis

Primary and secondary outcomes were evaluated using a Mann-Whitney *U* test. Differences in baseline characteristics between groups were evaluated using Fisher's exact test for dichotomous variables and Mann-Whitney *U* test for continuous variables. Descriptive statistics were used to evaluate AUC_{SBPe} in each study drug group. Statistical significance was defined as $p < 0.05$. Data were evaluated using R statistical software, version 3.3.1 (R Core Team, Vienna, Austria).

4. Results

A total of 39 patients (clevidipine, 10; SNP, 29) were screened with 14 patients (clevidipine, 8; SNP, 6) included in the final analysis (Fig. 1). Baseline characteristics were similar between groups (Table 1). The majority of patients were male (78.5%) and diagnosed with Stanford Type-B aortic dissection (54.1%). One patient in each study group received a one-time dose of labetalol intravenously (20 mg) prior to reaching SBP_{PT}.

Median time to reach SBP_{PT} goal was similar between clevidipine and SNP (1.68 versus 1.03 h, respectively [$p = 0.99$]). Median AUC_{SBPe} was not significantly different for clevidipine compared to SNP (206.9 vs 538.9 mm Hg $*$ min $*$ hr^{-1}, $p = 0.11$) (Table 1). Complete SBP data after initiation of study drug for all included patients is presented in Fig. 2. Six of 8 patients and 4 of 6 patients treated with clevidipine and SNP, respectively, had SBP_{PT} goal ranges of 100–120 mm Hg. Among these patients, the median AUC_{SBPe} differed for clevidipine compared to SNP, 159.1 vs 391.1 mm Hg $*$ min $*$ hr^{-1}, respectively. Median total duration of clevidipine and SNP infusion in the ICU was 46.6 h vs. 32.82 h, respectively.

Using AWP at time of study analysis, cost of study drug differed significantly between clevidipine and SNP (Table 1). Comparing cumulative drug cost per day, clevidipine cost significantly less ($885.84/day) compared to SNP ($4158/day [$p < 0.001$]). Costs for total number of punctured vials of clevidipine or compounded infusion bags of SNP continued to differ significantly between the groups (clevidipine, $1223.28/day; SNP, $7674.24/day [$p < 0.001$]).

5. Discussion

To our knowledge, this is the first study evaluating clevidipine use in acute aortic dissection. Rapid and effective control of SBP in acute aortic dissection is critically important to limiting progression of disease and occurrence of complications. Time to reach SBP_{PT} was similar for both clevidipine and SNP. Using AUC_{SBPe} as a surrogate marker for intensity and time spent outside of SBP_{PT} goals, the two drugs were also similar in terms of total time spent with proper BP control.

While efficacy data were similar between the two drugs, cost data were not. Use of clevidipine was associated with significantly reduced

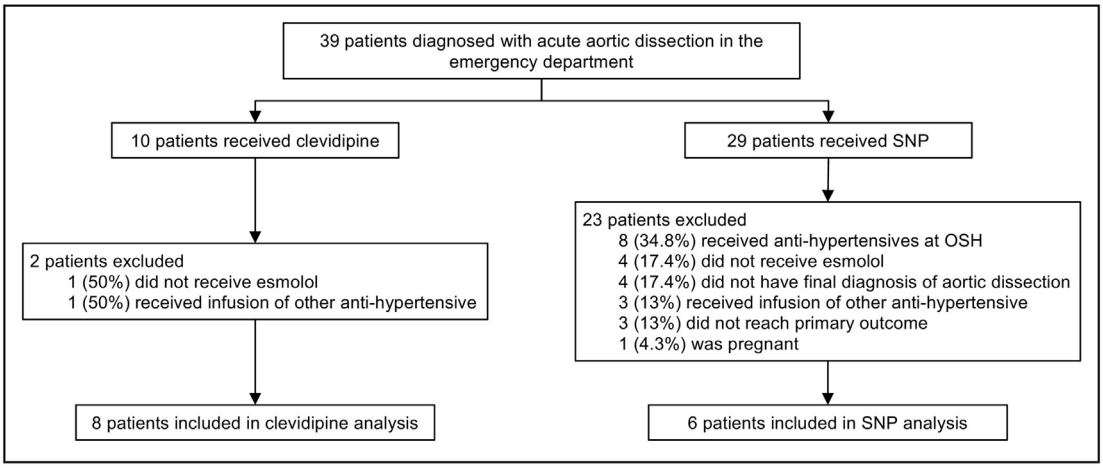

Fig. 1. Study enrollment flowchart. OSH, outside hospital; SNP, sodium nitroprusside.

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